tion of the residue gave a pale yellow oil, b.p. 97–102° (0.4 mm.), $n^{25}D$ 1.4645.

Anal. Calcd. for $C_{12}H_{21}NO_2$ (mol. wt., 211): C, 68.3; H, 10.0; N, 6.6. Found: C, 68.4; H, 9.8; N, 6.6.

H. 1-Benzyl-3,3-diethyl-2,4-pyrrolidinedione (VIII).—A solution of 43 g. of benzylamine in 200 ml. of ether was interacted with 53 g. of the bromoacetoacetate in accordance with the procedure described under G to give a colorless liquid, b.p. 145° (0.55 mm.), $n^{26}D$ 1.5235.

Anal. Calcd. for $C_{15}H_{19}NO_2$ (mol. wt., 245): C, 73.5; H, 7.8; N, 5.7. Found: C, 73.8; H, 8.0; N, 5.9.

Derivatives of 3,3-Dimethylpyrrolidinedione. A. 1-(Carbethoxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (IX).—A solution of 30 g. of ethyl glycinate in 25 ml. of benzene was treated with 34.5 g. of ethyl γ-bromo-α,α-dimethylacetoacetate[2] in 25 ml. of benzene in accordance with the procedure described under A above for the diethylacetoacetate. The product was a colorless liquid, b.p. 112° (0.2 mm.), $n^{26}D$ 1.4634, which tended to solidify to a low melting solid.

Anal. Calcd. for $C_{10}H_{15}NO_4$ (mol. wt., 213): C, 56.4; H, 7.0. Found: C, 56.3; H, 7.0; sapon. equiv., 188.

B. 1-(Carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X).—The ester (IX, 5 g.) was hydrolyzed as described for the diethyl analog with 12 ml. of 2 *N* NaOH to give the acid in the form of small white needle clusters (from ethyl acetate), m.p. 128–130°; infrared analysis showed a band for a strained carbonyl at 1765 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{11}NO_4$ (mol. wt., 185): C, 51.8; H, 5.9. Found: C, 52.0; H, 6.1.

C. 1,3,3-Trimethyl-2,4-pyrrolidinedione (XII).—A mixture of 200 g. of methylamine in ethanol (30% solution) was dissolved in 1000 ml. of ether and treated with 200 g. of the bromoacetoacetate according to the procedure previously described for the diethyl analog to give a colorless liquid, b.p. 141–144° (46 mm.), $n^{26}D$ 1.4720. The liquid partially solidified on standing. It was therefore chilled and filtered; the crystalline material was recrystallized from an ether–petroleum ether (b.p. 40–60°) mixture to give soft white crystals, m.p. 47–50°.

Anal. Calcd. for $C_7H_{11}NO_2$ (mol. wt., 141): C, 59.7; H, 7.8; N, 9.9. Found: C, 59.6; H, 7.7; N, 9.9.

The same compound could be made by decarboxylation of 1-(carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X). The product so obtained was treated with phenylhydrazine in the conventional manner to give yellow flakes (from ethanol) of 1,3,3-trimethyl-4-phenylhydrazono-2-pyrrolidone (XI), m.p. 167–173° (with prior softening).

Anal. Calcd. for $C_{13}H_{17}N_3O$ (mol. wt., 231): C, 67.5; H, 7.4. Found: C, 67.8; H, 7.6.

D. 1,3,3-Trimethyl-4-isonitroso-2-pyrrolidone (XIII).—A mixture of 10 g. of the dione (XII), 12 g. of hydroxylamine hydrochloride, 60 ml. of pyridine, and 60 ml. of ethanol was interacted as described for the diethyl analog to give small white needles of the product (from dilute ethanol), m.p. 211–212°.

Anal. Calcd. for $C_7H_{12}N_2O_2$ (mol. wt., 156): C, 53.8; H, 7.7; N, 18.0. Found: C, 53.8; H, 7.2; N, 18.1.

E. 1,3,3-Trimethyl-4-phenylsulfonamido-2-pyrrolidone (XIV).—A solution of 8 g. of the isonitroso compound (XIII) in methanol was reduced, and the reduction product was treated with benzenesulfonyl chloride in the manner previously described for the diethyl analog to give white spires (from dilute ethanol) of the product, m.p. 163–165°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3S$ (mol. wt., 282): C, 55.3; H, 6.4. Found: C, 55.4; H, 6.3.

Acknowledgment.—The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the infrared studies.

5*H*-1,4-Benzodiazepin-5-ones. Ring-Closure Reactions of Substituted 2-Aminobenzamides

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Several new 5*H*-1,4-benzodiazepin-5-ones were prepared from 2-aminobenzamides by ring closures involving intramolecular eliminations of alkylsulfonic or arylsulfonic acids, cyclodehydrochlorination, and cyclodehydration reactions. Some chemical transformations of the new compounds are presented.

During recent years, considerable effort has been expended toward the synthesis of 1*H*-1,4-benzodiazepines,[1] a group of compounds having interesting psychopharmacologic properties. In the course of our investigations into the preparation of centrally active drugs, we arrived at several routes for preparing novel 5*H*-1,4-benzodiazepin-5-ones through ring closures involving elimination reactions in suitably substituted 2-aminobenzamides.[2]

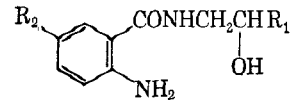
The first method involved the reaction of a 2-amino-*N*-(2-hydroxyalkyl)benzamide (I) with an alkylsulfonyl or arylsulfonyl chloride. The method is illustrated best by the preparation of 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIj). 2-Amino-*N*-(2-hydroxyethyl)benzamide (Ie), obtained from the reaction of 2-aminoethanol with isatoic anhydride, was treated with 2 molar equiv. of *p*-toluenesulfonyl chloride at 0–5° in pyridine. After several hours, the addition of water to the reaction mixture resulted in the precipitation of a solid which, on heating in ethanol, gave IIIj. It subsequently was shown that the cyclization occurred during the attempted purification of intermediate II, since the solid initially obtained had an infrared absorption spectrum significantly different from IIIj. The spectrum of the rather labile intermediate has an amide II band at 6.4 μ and is compatible with the open-chain structure of the *p*-toluenesulfonate ester of 2-*p*-toluenesulfonamido-*N*-(2-hydroxyethyl)benzamide. The amide II band is absent in the spectrum of IIIj, as expected, since it is a cyclic amide. The same reaction was carried out in stepwise fashion using 1 equiv. of *p*-toluenesulfonyl chloride. The product isolated was *N*-(2-hydroxyethyl)-2-*p*-toluenesulfonamidobenzamide. When the latter product in pyridine was treated with a 2nd molar equiv. of *p*-toluenesulfonyl chloride and the reaction worked up in the customary manner, IIIj again was obtained.

(1) (a) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962); (c) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962); (d) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Chem.*, **5**, 63 (1962); (e) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962); (f) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(2) M. Uskoković, J. Iacobelli, and W. Wenner [*ibid.*, **27**, 3606 (1963)] have described the preparation of 3*H*-1,4-benzodiazepin-2,5(1*H*,4*H*)-diones from substituted 2-aminobenzamides.

TABLE I

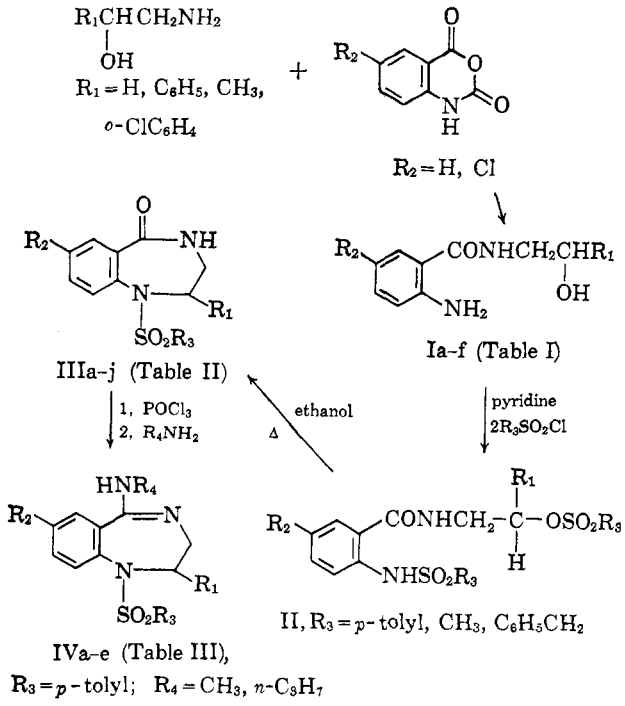
2-AMINO-N-(2-HYDROXYALKYL)BENZAMIDES



Compound I	R_1	R_2	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
a	H	Cl	120.5–122	C	87	$C_9H_{11}ClN_2O_2$	50.36	5.16	13.05	16.52	50.25	5.25	13.05	16.50
b	C_6H_5	Cl	119–121	A	55	$C_{15}H_{15}ClN_2O_2$	61.96	5.20	9.64	12.19	62.02	5.24	9.38	12.07
c	CH_3	Cl	109–110.5	A	83	$C_{10}H_{13}ClN_2O_2$	52.52	5.73	12.25	15.50	52.72	5.89	12.29	15.50
d	o-ClC_6H_4	Cl	105–107	B–A	80	$C_{16}H_{14}ClN_2O_2$	55.40	4.34	8.62	21.80	55.71	4.25	8.38	21.50
e[b]	H	H	90–91	B	38	$C_9H_{12}N_2O_2$	59.98	6.71	15.55		59.76	6.62	15.47	
f	o-ClC_6H_4	H	103–105	B–A	55	$C_{15}H_{15}ClN_2O_2$	61.97	5.20	9.63	12.19	62.22	5.00	9.34	11.6

[a] A = benzene, B = cyclohexane, and C = water. [b] D. R. Shridar and K. S. Narang [*J. Indian Chem. Soc.*, **33**, 305 (1956)] reported m.p. 95° for Ie.

CHART I



The compounds Ia–f (Table I) were converted to IIIa–j (Table II) as described above. (See Chart I.)

In each of these cyclization reactions, the formation of a 5*H*-1,4-benzodiazepin-5-one was accompanied by distinct infrared spectral changes. Compounds IIIa–j have only weak absorptions in the normal NH stretching region (3.0 μ) and no amide II band (6.4 μ). These bands are clearly present in the spectra of benzamides Ia–f. Another noticeable change is the appearance of a broad absorption at 3.5–3.6 μ which is not present in the latter compounds.

With the exception of the instance where $R_1 = CH_3$, $R_2 = Cl$, and $R_3 = p$-tolyl in II, none of the intermediates was sufficiently stable to be purified by recrystallization. It was necessary to treat this ester with 1 equiv. of sodium methoxide in boiling methanol before ring closure to 7-chloro-1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIc) would occur.

In another experiment, treatment of 2-amino-5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)benzamide (Id) with 2 molar equiv. of *p*-toluenesulfonyl chloride gave 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide instead of the expected cyclized product. Apparently, the 2nd equiv. of *p*-toluenesulfonyl chloride did not react with the somewhat sterically hindered hydroxyl group of Id. When a more reactive reagent, methanesulfonyl chloride, was allowed to react with 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide, ring closure occurred and resulted in the formation of 7-chloro-2-(*o*-chlorophenyl)-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIId).

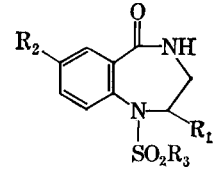
The foregoing experiments make it clear that the amino group of I reacts with the 1st equiv. of sulfonyl chloride, forming a sulfonamide. The 2nd equiv. reacts with the hydroxyl function, resulting in a sulfonate ester (II). Merely heating II in ethanol results in a surprisingly facile elimination of R_3SO_2OH. This elimination probably occurs by a concerted backside displacement of the OSO_2R_3 anion by the sulfonamido nitrogen with simultaneous abstraction of a proton from the same nitrogen atom. In only one experiment was the addition of a strong base, sodium methoxide, necessary to promote this elimination and concurrent cyclization to IIIc. It is difficult to assess the significance of the one exception since, in all other cases, elimination and ring closure occurred merely by heating the intermediate II.

N-Phenylanthranilic acid reacted with ethyl chloroformate to give *N*-phenylisatoic anhydride. Treatment of the anhydride with 2-aminoethanol afforded 2-anilino-*N*-(2-hydroxyethyl)benzamide. The latter compound in pyridine was treated with 1 equiv. of methanesulfonyl chloride. After standing several hours, the reaction mixture was treated with water, resulting in the separation of 1,2,3,4-tetrahydro-1-phenyl-5*H*-1,4-benzodiazepin-5-one. In this reaction the methanesulfonyl chloride reacts preferentially with the hydroxyl group, since the basicity of the amino nitrogen is considerably reduced by the presence of the two aromatic moieties to which it is bonded.

Removal of the *p*-tolylsulfonyl group from compound IIIj was accomplished by sulfuric acid hydrolysis. The product isolated was 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one. In similar fashion, hydrolysis of 7-chloro-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIa) afforded 7-chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one.

TABLE II

1-ALKYLSULFONYL- AND 1-ARYLSULFONYL-1,2,3,4-TETRAHYDRO-5*H*-1,4-BENZODIAZEPIN-5-ONES

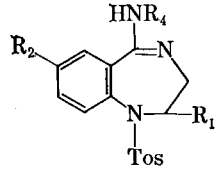


Compound III	R_1	R_2	R_3	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd., % C	H	N	Cl	S	Found, % C	H	N	Cl	S
a	H	Cl	C_7H_7[b]	174–176	D	34	$C_{16}H_{15}ClN_2O_3S$	54.78	4.31	7.98	10.10	9.14	54.94	4.37	8.00	10.2	9.16
b	C_6H_5	Cl	C_7H_7	132–133	E	54	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	62.09	4.58	6.74	8.4	7.7
c	CH_3	Cl	C_7H_7	122–124	E	55	$C_{17}H_{17}ClN_2O_3S$	55.96	4.70	7.68	9.72	8.79	55.95	4.59	7.63	9.8	8.99
d	*o*-ClC_6H_4	Cl	C_7H_7	165–166	A–F	40	$C_{22}H_{18}Cl_2N_2O_3S$	57.27	3.93	6.07	15.37	6.95	57.54	3.79	5.90	15.3	7.2
e	H	H	CH_3	164–165.5	D	22	$C_{10}H_{12}N_2O_3S$	49.88	5.03	11.66		13.34	50.08	5.05	11.42		13.4
f	CH_3	Cl	CH_3	114–116	D–C	23	$C_{11}H_{13}ClN_2O_3S$	45.75	4.54	9.70	12.28	11.10	46.00	4.54	9.49	12.36	11.1
g	C_6H_5	Cl	CH_3	157–158	E	75	$C_{16}H_{15}ClN_2O_3S$	54.78	4.31	7.98	10.10	9.14	54.88	4.31	8.29	10.12	9.2
h	C_6H_5	Cl	$CH_2C_6H_5$	139–140	B	63	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	61.71	4.41	6.39	8.3	7.8
i	*o*-ClC_6H_4	H	C_7H_7	152–153.5	D	41	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	61.91	4.68	6.56	8.0	7.6
j	H	H	C_7H_7	197–199	D	78	$C_{16}H_{16}N_2O_3S$	60.74	5.14	8.85		10.14	60.96	5.32	9.11		10.0

[a] A = benzene, B = cyclohexane, C = water, D = ethanol, E = methanol, and F = petroleum ether. [b] C_7H_7 = *p*-tolyl.

TABLE III

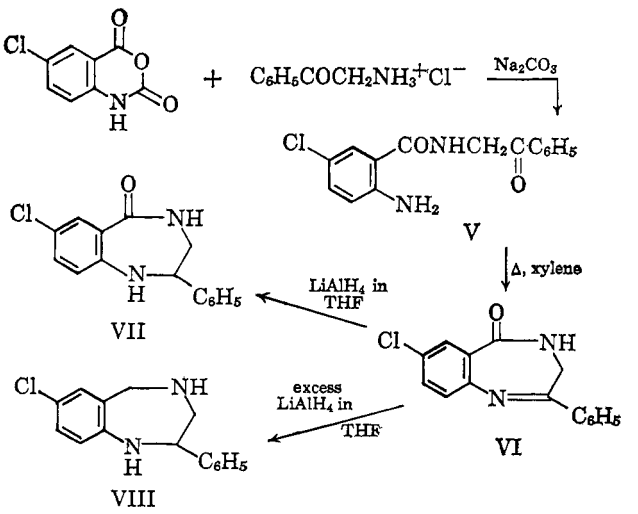
2,3-DIHYDRO-5-ALKYLAMINO-1-*p*-TOLYLSULFONYL-1*H*-1,4-BENZODIAZEPINES



Compound IV	R_1	R_2	R_4	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd. % C	H	N	Cl	S	Found, % C	H	N	Cl	S
a	H	H	CH_3	161–164	A	31	$C_{17}H_{19}N_3O_2S$	61.98	5.81	12.76		9.73	62.25	5.94	12.98		9.5
b[b]	H	H	*n*-C_3H_7	145–150	B	17	$C_{19}H_{23}N_3O_2S$	62.25	6.60	11.46		8.79	62.64	7.04	11.2		8.4
c	C_6H_5	Cl	CH_3	198–200	A	57	$C_{23}H_{22}ClN_3O_2S$	62.79	5.04	9.55	8.06	7.29	62.63	4.56	9.49	8.2	7.2
d	*o*-ClC_6H_4	Cl	CH_3	232–234	C	13	$C_{23}H_{21}Cl_2N_3O_2S$	58.23	4.46	8.86	14.94	6.76	57.90	4.52	8.82	14.60	6.95
e	*o*-ClC_6H_4	H	CH_3	172–174	C	23	$C_{23}H_{22}ClN_3O_2S$	62.79	5.04	9.55	8.06	7.29	63.02	5.23	9.46	8.0	7.4

[a] A = benzene, B = cyclohexane, and C = ethanol. [b] Analyzed as hemihydrate.

CHART II



Treatment of IIIj with phosphorus pentasulfide in pyridine gave 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepine-5-thione.

7-Chloro-2,3-dihydro-5-methylamino-2-phenyl-1-*p*-tolylsulfonyl-1*H*-1,4-benzodiazepine (IVc) was obtained by reaction of 7-chloro-1,2,3,4-tetrahydro-2-phenyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIb) with phosphorus oxychloride, followed by treatment of the product with methylamine. Other examples are given in Table III.

Another synthetic route to 5*H*-1,4-benzodiazepin-5-ones was through cyclodehydrochlorination. For example, reaction of 2-amino-5-chloro-*N*-(2-hydroxyethyl)benzamide with thionyl chloride gave 2-amino-5-chloro-*N*-(2-chloroethyl)benzamide. Heating the latter compound in boiling *N*,*N*-dimethylformamide in the presence of sodium carbonate gave 7-chloro-1,2,-3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one. Infrared spectral comparison of the latter product with the hydrolysis product of IIIa, previously described, showed the two materials to be identical. A mixture melting point of the two also confirmed this identity.

Treatment of an aqueous solution of ω-aminoacetophenone hydrochloride with sodium carbonate, followed by the addition of 5-chloroisatoic anhydride, afforded 2-amino-5-chloro-*N*-phenacylbenzamide (V). Cyclodehydration of V to 7-chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VI) was accomplished by heating V in boiling xylene solution. Lithium aluminum hydride reduction of VI in tetrahydrofuran gave 7-chloro-1,2,3,4-tetrahydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VII) by reduction of the azomethine bond. When a large excess of hydride was used and the reaction time was extended, both the azomethine and lactam bonds were reduced, giving 7-chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (VIII). (See Chart II.)

In contrast to the present work, Sulkowski and Childress[3] reported that the lithium aluminum hydride reduction of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, an isomer of VI, left the azomethine bond unchanged but reduced the lactam instead. The product of their reduction was 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine. Sternbach and coworkers[4] reported the same observations but they subsequently were able to reduce the azomethine bond of the latter compound by a second treatment with lithium aluminum hydride. The greater ease with which the azomethine bond in VI is reduced, however, compared with the lactam bond is not unexpected since it is an anilic type. It is well established that anils undergo reduction readily under these conditions. The aromatic lactam carbonyl group, on the other hand, requires slightly more vigorous conditions for reduction.

The pharmacologic properties of these 5*H*-1,4-benzodiazepin-5-ones and their derivatives are currently under investigation.

(3) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963).

Experimental[5]

1,2,3,4-Tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIj).—To an ice-cold solution of 8.4 g. of 2-amino-*N*-(2-hydroxyethyl)benzamide (Ie) in 30 ml. of dry pyridine was added, in portions, 19 g. of *p*-toluenesulfonyl chloride. After standing overnight in the refrigerator, the reaction mixture was poured into 100 ml. of water. The oily residue was washed several times with water, affording a crystalline product (19.6 g.), m.p. 94–99°. This material (14.5 g.) was added to 50 ml. of ethanol and the mixture was heated for 15 min. on the steam bath. After cooling in ice, the crystalline product was washed with 50 ml. of hot water, affording 8.5 g. of IIIj, m.p. 192–197°. The analytical sample obtained by recrystallization from ethanol had m.p. 197–199°; λ_{max} 6.14 (C=O), 7.51, and 8.65 μ (SO_2).

***N*-(2-Hydroxyethyl)-2-*p*-toluenesulfonamidobenzamide.**—To a cold solution of 2 g. of Ie in 15 ml. of dry pyridine was added 2.1 g. of *p*-toluenesulfonyl chloride. The mixture was allowed to stand 3 hr. in the refrigerator and was then poured into 100 ml. of water. The viscous oil which separated crystallized on cooling to afford 3.0 g. of product, m.p. 115–117°. Two recrystallizations from benzene raised the melting point to 125.5–126.5° and gave λ_{max} 6.15 (C=O), 6.47 (amide II), 7.50, and 8.68 μ (SO_2).

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.58; H, 5.25; N, 8.47; S, 9.3.

5-Chloro-*N*-(2-hydroxypropyl)-2-(*p*-toluenesulfonamido)benzamide, *p*-Toluenesulfonate Ester.—To an ice-cold solution of 8.4 g. of 2-amino-5-chloro-*N*-(2-hydroxypropyl)benzamide (Ic) in 25 ml. of dry pyridine was added 14 g. of *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand overnight at room temperature and was then poured into 200 ml. of warm water. The oily residue which was deposited was washed several times with water. The addition of a little methanol resulted in the formation of a crystalline solid (4.7 g.), m.p. 120–123°. The analytical sample obtained by recrystallization from ethanol had a m.p. 116–118°; λ_{max} 6.09 (C=O), 6.52 (amide II), 7.44, and 8.64 μ (SO_2).

Anal. Calcd. for $C_{24}H_{25}ClN_2O_6S_2$: C, 53.67; H, 4.69; Cl, 6.60; N, 5.22; S, 11.94. Found: C, 53.90; H, 4.77; Cl, 6.7; N, 5.47; S, 11.9.

7-Chloro-1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIc).—To a solution of 3.5 g. of 5-chloro-*N*-(2-hydroxypropyl)-2-(*p*-toluenesulfonamido)benzamide, *p*-toluenesulfonate ester, in 25 ml. of anhydrous methanol was added 0.5 g. of sodium methoxide. The reaction mixture was heated under reflux for 10 min. and was then cooled in ice. The solid which deposited was washed with water. Recrystallization from methanol gave 1.3 g. of product, m.p. 122–124°; λ_{max} 6.11 (C=O), 7.52, and 8.76 μ (SO_2).

***o*-Chloromandelonitrile Acetate.**—A solution of 134 g. of *o*-chloromandelonitrile in 82 g. of acetic anhydride was heated under reflux for 2 hr. The reaction mixture was distilled *in vacuo* through a Claisen head. The product, which was the fraction distilling between 109 and 111° (0.25 mm.), amounted to 107 g. and had λ_{max} 5.67 μ (C=O).

(4) L. H. Sternbach, E. Reeder, and G. A. Archer, *ibid.*, **28**, 2456 (1963).

(5) Melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were determined in potassium bromide pellets using a Perkin-Elmer, Model 21, spectrophotometer.

Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.84; Cl, 16.92; N, 6.68. Found: C, 57.30; H, 3.92; Cl, 17.2; N, 6.47.

o-Chloro-β-hydroxyphenethylamine.—To a cold, stirred suspension of 37.9 g. of lithium aluminum hydride in 800 ml. of dry tetrahydrofuran was added a solution of 107 g. of *o*-chloromandelonitrile acetate in 50 ml. of tetrahydrofuran over a period of 1 hr. The reaction mixture was allowed to stand for 20 min. at room temperature and was then heated under reflux for 2 hr. The aluminum complex was decomposed cautiously, after cooling in ice, by the dropwise addition of 100 ml. of water followed by 200 ml. of 20% sodium hydroxide solution. The reaction mixture was filtered and the filtrate was concentrated by evaporation *in vacuo* on a rotary evaporator. The oily residue was distilled through a Claisen head, affording 56 g. of product, b.p. 108–112° (0.25 mm.). The product was used without further purification.

5-Chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido) benzamide.—To an ice-cold solution of 20 g. of 2-amino-5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)benzamide (Id) in 40 ml. of dry pyridine was added 23 g. of *p*-toluenesulfonyl chloride. After standing overnight in the refrigerator, the reaction mixture was poured into 200 ml. of water. The oily layer was washed several times with water. The addition of a little methanol induced crystallization. The crude product amounted to 23 g., m.p. 70–92°. Several recrystallizations from benzene raised the melting point to 165–166° and gave λ_{max} 6.10 (C=O), 6.46 (amide II), 7.42, and 8.61 μ (SO_2).

Anal. Calcd. for $C_{22}H_{20}Cl_2N_2O_4S$: C, 55.12; H, 4.20; Cl, 14.79; N, 5.82. Found: C, 55.28; H, 4.10; Cl, 14.5; N, 5.98.

7-Chloro-2-*o*-chlorophenyl-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIId).—To an ice-cold solution of 5.2 g. of 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide in 10 ml. of anhydrous pyridine was added, dropwise, 1.26 g. of methanesulfonyl chloride. The temperature of the reaction was kept below 20° during the addition. After the reaction mixture was allowed to stand 3.5 hr. at room temperature, ice was added. The gummy residue which was deposited was dissolved in benzene. The benzene was removed by evaporation leaving an oily residue. Trituration of the residue with petroleum ether (b.p. 30–60°) gave a crystalline product (2 g.), m.p. 155–163°. Recrystallization from benzene–petroleum ether raised the melting point to 165–166° and gave λ_{max} 6.07 (C=O), 7.48, 7.56 doublet, and 8.61 μ (SO_2).

***N*-Phenylisatoic Anhydride.**—A solution of 5 g. of *N*-phenylanthranilic acid in 20 ml. of ethyl chloroformate was heated under reflux for 10 hr. The excess ethyl chloroformate was removed *in vacuo* on a rotary evaporator. The residual solid amounted to 3.6 g., m.p. 172–179°. Recrystallization of the product from ethanol raised the melting point to 177–179°, and gave λ_{max} 5.64 and 5.76 μ (anhydride).

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.21; H, 3.83; N, 5.65.

2-Anilino-*N*-(2-hydroxyethyl)benzamide.—To a solution of 10 g. of *N*-phenylisatoic anhydride in 50 ml. of absolute ethanol was added 2.6 g. of 2-aminoethanol. The reaction mixture was heated for 10 min. on the steam bath. The ethanol was removed *in vacuo* on a rotary evaporator leaving a solid residue (8.1 g.), m.p. 62–70°. Recrystallization from benzene–cyclohexane raised the melting point to 77–79° and gave λ_{max} 6.16 (C=O), 6.52 μ (amide II).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.04; H, 6.11; N, 10.92.

1,2,3,4-Tetrahydro-1-phenyl-5*H*-1,4-benzodiazepin-5-one.—To an ice-cold solution of 2.6 g. of 2-anilino-*N*-(2-hydroxyethyl) benzamide in 5 ml. of dry pyridine was added, dropwise and with stirring, 1.1 g. of methanesulfonyl chloride, keeping the temperature of the reaction at 0–10°. After the reaction mixture had warmed to room temperature, ice was added. The crystalline product which was deposited amounted to 2.2 g., m.p. 60–64°. Recrystallization from aqueous ethanol raised the melting point to 66–68° and gave λ_{max} 6.10 μ (C=O).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.57; H, 5.92; N, 11.53.

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-one.—A solution of 1 g. of IIIj in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 5 days. The reaction mixture was then poured into 15 ml. of water and the solution was neutralized with 3 *N* sodium hydroxide solution. A crystalline material was deposited (0.2 g.), m.p. 52–54°. Recrystallization from *n*-pentane afforded 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one, m.p. 55°; λ_{max} 6.15 μ (C=O).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.47; H, 5.92; N, 17.06.

1,2,3,4-Tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepine-5-thione.—To a solution of 1 g. of IIIj in 15 ml. of dry pyridine was added 1 g. of phosphorus pentasulfide. The reaction mixture was heated under reflux for 2 hr., cooled in ice, and poured into 50 ml. of hot water. The aqueous solution was neutralized with 30% hydrochloric acid. The crystalline product which was deposited amounted to 1.3 g., m.p. 140–154°. Recrystallization from aqueous pyridine raised the melting point to 160–163° and gave λ_{max} 7.51 and 8.67 μ (SO_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 57.80; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.91; H, 4.84; N, 8.43; S, 19.1.

7-Chloro-2,3-dihydro-5-methylamino-2-phenyl-1-*p*-tolyl-sulfonyl-1*H*-1,4-benzodiazepine (IVc).—A solution of 7.7 g. of 7-chloro-1,2,3,4-tetrahydro-2-phenyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIb) in 35 ml. of phosphorus oxychloride was heated under reflux for 2 hr. The excess phosphorus oxychloride was removed *in vacuo* on a rotary evaporator. The residual oil was cooled in ice. A cold solution of methanolic methylamine (10 g. of methylamine in 25 ml. of anhydrous methanol) was added, dropwise, to the residue. The reaction mixture was then heated under reflux for 30 min. After removal of the excess methylamine and solvent by evaporation, 25 ml. of water was added to the residue. A yellow, amorphous substance (9.4 g.) was obtained which, after recrystallization from benzene, gave 4.5 g. of product, m.p. 198–200°; λ_{max} 7.84 and 8.86 μ (SO_2).

2-Amino-5-chloro-*N*-(2-chloroethyl)benzamide.—A solution of 13.4 g. of 2-amino-5-chloro-*N*-(2-hydroxyethyl)benzamide (Ia) in 100 ml. of thionyl chloride was heated under reflux for 1 hr. The excess thionyl chloride was removed *in vacuo* on a rotary evaporator. The residual solid was treated with 10% sodium bicarbonate solution. The solid was recrystallized from cyclohexane, affording 2.4 g. of product, m.p. 115–116°; λ_{max} 6.16 (C=O) and 6.54 μ (amide II).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$: C, 46.37; H, 4.32; Cl, 30.42; N, 12.02. Found: C, 46.52; H, 4.43; Cl, 30.40; N, 12.01.

7-Chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one.—To a solution of 6.2 g. of 2-amino-5-chloro-*N*-(2-chloroethyl)benzamide in 15 ml. of *N*,*N*-dimethylformamide was added 4 g. of finely pulverized sodium carbonate. The reaction mixture was heated under reflux for 1.5 hr. and filtered, and water was added to the filtrate until precipitation of the product was complete. Recrystallization from *n*-hexane afforded 3.2 g. of product, m.p. 76–78°; λ_{max} 6.12 μ (C=O).

Anal. Calcd. for $C_9H_9ClN_2O$: C, 54.97; H, 4.61; Cl, 14.25; N, 18.03. Found: C, 55.26; H, 4.52; Cl, 14.48; N, 18.00.

The identical product, m.p. 77–78°, was obtained by hydrolysis of IIIa in concentrated sulfuric acid for 24 hr. at ambient temperature. A mixture melting point of the two materials gave no depression. The infrared spectra were identical.

2-Amino-5-chloro-*N*-phenacylbenzamide (V).—To a stirred solution of 15 g. of ω-aminoacetophenone hydrochloride in 60 ml. of water was added 17.3 g. of 5-chloroisoatoic anhydride, followed by 4.7 g. of sodium carbonate. The reaction mixture was allowed to stand overnight, with stirring, at room temperature. Filtration afforded 25.1 g. of product, m.p. 130–140°. Recrystallization from cyclohexane–benzene raised the melting point to 148–150° and gave λ_{max} 5.91, 6.09 (C=O) and 6.62 μ (amide II).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70. Found: C, 62.70; H, 4.51; Cl, 12.2; N, 9.59.

7-Chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VI).—A suspension of 5.9 g. of V in 150 ml. of dry xylene was heated, with stirring, to the boiling point. The water liberated was collected in a Dean–Stark water separator. The reaction mixture was then filtered and the filtrate was cooled in ice affording a crystalline product (2.5 g.), m.p. 155–165°. Recrystallization from xylene gave VI, m.p. 160–162°; λ_{max} 6.01 μ (C=O).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.09; Cl, 13.10; N, 10.35. Found: C, 66.83; H, 4.37; Cl, 12.55; N, 10.16.

7-Chloro-1,2,3,4-tetrahydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VII).—To a stirred, ice-cold suspension of 1.14 g. of lithium

aluminum hydride in 200 ml. of anhydrous tetrahydrofuran was added, dropwise, a solution of 5.5 g. of VI in 50 ml. of anhydrous tetrahydrofuran. When the addition was completed, the reaction mixture was stirred at room temperature for 2 hr. and then was heated under reflux for 1 hr. The reaction mixture was cooled in ice, and 50% aqueous tetrahydrofuran (30 ml.) was added cautiously, followed by 25 ml. of 10% sodium hydroxide solution. The reaction mixture was filtered and the filtrate was taken to dryness on a rotary evaporator. The oily residue which was deposited was triturated with 15 ml. of ethyl acetate resulting in a crystalline product (1.8 g.), m.p. 159–166°. Recrystallization from ethyl acetate afforded VII, m.p. 170–173°; λ_{max} 6.10 μ (C=O).

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 65.88; H, 4.67; Cl, 12.55; N, 10.36.

7-Chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (VIII).—The reduction of 10.8 g. of VI with 4.6 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran was carried out as described in the previous example, except that the reaction mixture was heated under reflux for 3.5 hr. before work-up. Recrystallization from methanol resulted in a hygroscopic product (2.5 g.), m.p. 60–68°.

Anal. Calcd. for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.84; N, 10.83. Found: C, 69.33; H, 6.13; N, 10.43.

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Ethyl Hydantoin-5-carboxylates[1-3]

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Ethyl hydantoin-5-carboxylates have been prepared from ureidomalonates in the presence of sodium ethoxide.

Hydantoins and structurally related compounds, natural and synthetic, are legion in the chemical literature. There are, however, few specific references to derivatives of hydantoin-5-carboxylic acid. This acid, as would be predicted because of its structural relationship to malonic and acetoacetic acids, possesses a reactive substituted methylene group and is difficult to isolate owing to ready decarboxylation. Amides of substituted hydantoin-5-carboxylic acid were isolated by both Fischer[5] and Biltz[6,7] as degradation products of methylated purines. In most cases, attempts to isolate acids from these amides were thwarted by decarboxylation. Biltz,[7] however, isolated 3-methylhydantoin-5-carboxylic acid which was decarboxylated when heated to 130°.

Johnson and Nicolet[8] prepared hydantoin-5-carboxamide (VI) by the ring closure of N-carbethoxyaminomalonamide. The compound was not investigated further except to fuse it with urea in an attempt to prepare uric acid. Johnson and Nicolet also attempted to prepare the intermediate, pseudouric acid, by the reaction of ethyl ureidomalonate (I) and urea in the presence of sodium ethoxide. An alcohol-insoluble precipitate formed which was described as "the sodium salt of ethyl ureidomalonate."

The potential of this latter reaction led us to repeat Johnson's experiment with a variety of ureidomalonates which were readily prepared by the addition of ethyl aminomalonate to the appropriate isocyanate.

When treated with sodium ethoxide, the ureidomalonates cyclize. Under these conditions, ethyl ureidomalonate gave the stable sodium salt of ethyl hydantoin-5-carboxylate (II). The isolation of the parent ester was technically difficult. Initially, ring closure of ethyl ureidomalonate was demonstrated by (1) failure to regenerate ethyl ureidomalonate from the sodium salt on acidification, (2) conversion of the salt to hydantoin (IV) by digestion with concentrated hydrochloric acid, and (3) conversion of the salt to the amide (VI) by cold concentrated ammonium hydroxide.

In alcohol–water solutions, an irreversible change can be observed in the ultraviolet spectrum of I in the region 210–230 mμ on treatment with base followed by acidification. Since no change occurs in the spectrum of I on direct treatment with acid, it was assumed that cyclization occurred on treatment with base. Cyclization occurred so rapidly in basic solution that it was not possible to record the spectrum of the ethyl ureidomalonate anion. Elemental analysis of the sodium salt and successful isolation of the ester III by neutralization with acid-form Dowex-50 resin confirmed ring closure.

The ultraviolet spectra of ethyl hydantoin-5-carboxylates have a strong maximum in the region 290–310 mμ in basic alcohol–water solutions (Table I). The maximum fades rapidly and in this respect these substances have spectral properties similar to those of diethyl malonate and ethyl acetoacetate. Ionization on the 5-position is indicated. The rapid fading of the maximum is due to the saponification of the ester to the corresponding hydantoin-5-carboxylate anion.

Although in sodium ethoxide the cyclization of I occurred at room temperature, reflux was employed to obtain a more easily filtered product. The cyclization of ethyl N′-phenylureidomalonate, however, was a slower reaction and reflux in ethanol was necessary to obtain a good yield of ethyl 3-phenylhydantoin-5-carboxylate (VIII).

Ethyl N′-tetra-O-acetylglucosylureidomalonate formed an insoluble salt when treated with alcoholic

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