[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Diuretics. V. 3,4-Dihydro-1,2,4-benzothiadiazine 1,1-Dioxides

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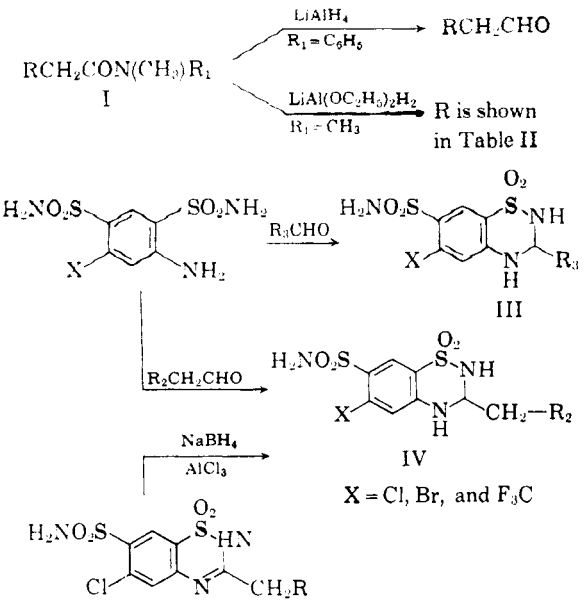
The synthesis and properties of thirty new 3-cycloalkene and 3-cycloalkane-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides are described. Correlations between their structure and biological activity confirm previously proposed analogies between similarly 3-substituted 3,4-unsaturated and 3,4-dihydro derivatives of the benzothiadiazine 1,1-dioxide nucleus.

This paper describes the synthesis of new cycloalkene and cycloalkane acetaldehydes and the condensation of these aldehydes and cycloalkene carboxaldehydes with 4-amino-6-halo- and 4-amino-6-trifluoromethylbenzene-1,3-disulfonamides to yield 3-cycloalkene and 3-cycloalkane derivatives of 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide. The purpose of this investigation was to confirm the premise of the preceding paper wherein the saluretic and diuretic activities of these 3,4-dihydro compounds could be anticipated.

Cycloalkanones were allowed to react with cyanoacetic acid to yield 1-cycloalkenylacetonitriles. Catalytic hydrogenation of 1-cycloalkenylacetonitriles gave cycloalkylacetonitriles. Acid hydrolysis of cycloheptylacetonitrile, 3-methylcyclopentylacetonitrile, 1-cyclohexenylacetonitrile, and 1-cyclopentenylacetonitrile furnished the corresponding acetic acids. Distillation of 1-cyclopentene acetic acid caused a partial conversion of the acid to the lactone 2-ketohexahydrocyclopenta[b] furan. Acid hydrolysis of 1-cycloheptenylacetonitrile and 2-methyl-1- or 5-cyclopentenyl-acetonitrile formed only the lactones, 2-ketooctahydrocyclohepta[b]-furan and 2-keto-4- or 6$\alpha$-methylhexahydrocyclopenta[b]furan. The Grignard reagent prepared from 5-norbornylenylmethylbromide was carbonated to yield 5-norbornylenylacetic acid. Acid chlorides were obtained by thionyl chloride treatment of 2-cyclopentene-; 2-cyclohexene-, and 3-cyclohexene-acetic acids. The mixture of 1-cyclopentaneacetic acid and its lactone gave a 40% yield of 1-cyclopentenylacetyl chloride. *N*-Methylanilides (I. $R_1$ = $C_6H_5$) of 2-cyclopentene-, cyclopentane-, 1-cyclohexene-, 2-cyclohexene-, 3-cyclohexene-, cyclohexane-, 1-methylcyclohexane-, 3-methylcyclopentane-, cycloheptane-, and 5-norbornyleneacetic acids were reduced to the cycloalkene and cycloalkane acetaldehydes (II) with lithium aluminum hydride. *N,N*-Dimethylamides (I. $R_1$ = $CH_3$) of 2-cyclopentene- and 1-cyclohexeneacetic acids and lithium diethoxyaluminum hydride gave 2-cyclopentene- and 1-cyclohexeneacetaldehydes. Yields from the *N,N*-dimethylamide were lower than those obtained from the *N*-methylanilides. The aldehydes were characterized as semicarbazones and 2,4-dinitrophenylhydrazones. 5-Norbornylenylcarboxldehyde[1] and 6-methyl-5-norbornylenylcarboxaldehyde[2] were obtained by the methods described in the literature.

The cycloalkene and cycloalkane acetaldehydes and carboxaldehydes were allowed to react with 4-amino-6-chlorobenzene-1,3-disulfonamide, 4-amino-6-bromobenzene-1,3-disulfonamide, and with 4-amino-6-trifluoromethylbenzene-1,3-disulfonamide in the presence of mineral acid to afford the 3,4-dihydro-3-substituted-6-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxides (III and IV) listed in Tables III and IV. Attempted catalytic reduction of 6-chloro-3-cyclohexylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide failed to saturate the 3-4 double bond.[3]

In contrast to this sodium borohydride did reduce this compound as well as 6-chloro-3-cyclopentylmethyl - 7 - (*N* - methylsulfamoyl) - 1,2,4-benzothiadiazine 1,1-dioxide[3] and 6-chloro-3-cyclopentylmethyl - 7 - sulfamoyl - 1,2,4 - benzothiadiazine 1,1-dioxide[3] to yield 3,4-dihydro derivatives. The 3,4-dihydro-3-substituted 7-sulfamoyl - 1,2,4 - benzothiadiazine 1,1 - dioxides are characterized by an intense absorption band in




(1) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

(2) O. Diels and K. Alder, *Ann.*, **470**, 62 (1929).

(3) C. W. Whitehead, J. J. Traverso, F. J. Marshall, and D. Morrison *J. Org. Chem.*, **26**, 2809 (1961).

TABLE I

$RCH_2CON(CH_3)R_1$

| R | $R_1$ | Formula | Yield, % | B.P. | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| 2-Cyclopentenyl | $CH_3$ | $C_9H_{15}NO$ | 79 | 85 (0.25 mm.) | 70.55 | 9.87 | 9.14 | 70.04 | 9.43 | 8.82 |
| 1-Cyclohexenyl | $CH_3$ | $C_{10}H_{17}NO$ | 75 | 95 (0.4 mm.) | 71.81 | 10.25 | 8.38 | 71.32 | 9.58 | 8.19 |
| Cyclopentyl | $C_6H_5$ | $C_{14}H_{19}NO$ | 80 | 130 (1.0 mm.) | | | 6.45 | | | 6.59 |
| 1-Cyclohexenyl | $C_6H_5$ | $C_{15}H_{19}NO$ | 80 | 130 (0.3 mm.) | | | 6.11 | | | 6.22 |
| 2-Cyclohexenyl | $C_6H_5$ | $C_{15}H_{19}NO$ | 82 | 130 (0.3 mm.) | | | 6.11 | | | 6.30 |
| 3-Cyclohexenyl | $C_6H_5$ | $C_{15}H_{19}NO$ | 90 | 132 (0.3 mm.) | | | 6.11 | | | 6.20 |
| Cyclohexyl | $C_6H_5$ | $C_{15}H_{21}NO$ | 95 | 136 (0.4 mm.) | | | 6.05 | | | 5.96 |
| 3-Methylcyclopentyl | $C_6H_5$ | $C_{15}H_{21}NO$ | 88 | 104 (0.08 mm.) | 77.88 | 9.15 | | 77.48 | 9.12 | |
| 5-Norbornylenyl | $C_6H_5$ | $C_{16}H_{19}NO$ | 95 | 117 (0.08 mm.) | 79.63 | 7.94 | | 79.71 | 8.02 | |
| Cycloheptyl | $C_6H_5$ | $C_{16}H_{23}NO$ | 95 | 154 (1.0 mm.) | 78.36 | 9.45 | 5.71 | 78.52 | 9.56 | 5.66 |
| 1-Methylcyclohexyl | $C_6H_5$ | $C_{16}H_{23}NO$ | 98 | 151 (4.5 mm.) | 78.32 | 9.45 | 5.71 | 78.45 | 9.69 | 5.46 |

the infrared at approximately 6.2 $\mu$ and by two $pK_a$'s in aqueous 66% *N,N*-dimethylformamide of 11.0–11.4 and13.0–13.3. These criteria were used to confirm their structures.

$R_2$ is shown in Table III and $R_3$ in Table IV.

## EXPERIMENTAL

*1-Cycloalkenylacetonitriles.* The following 1-cycloalkenylacetonitriles were prepared according to the method described by Cope and co-workers.[4]

*1-Cycloheptenylacetonitrile.* Yield 81%, b.p. 104° at 11 mm. $n_D^{25}$ 1.4808 (reported[5] b.p. 121–122° at 23 mm., $n_D^{22}$ 1.4821).

*1-Cyclopentenylacetonitrile.* Yield 64%, b.p. 72–73° at 10 mm., $n_D^{25}$ 1.4672 (reported[6] b.p. 172–175°).

*3-Methyl-1- or 5-cyclopentenylacetonitrile.* Yield 80%, b.p. 78° at 10 mm., $n_D^{25}$ 1.4488 (reported[7] b.p. 82° at 10 mm., $n_D^{19}$ 1.45972).

*2-Methyl-1- or 5-cyclopentenylacetonitrile* Yield 79%, b.p. 83–84° at 11 mm., $n_D^{25}$ 1.4672.

*Anal.* Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.57; H, 9.15; N, 11.69.

*Cycloalkylacetonitriles.* A solution of 0.8 mole of the 1-cycloalkenylacetonitrile in 200 ml. of ethanol was hydrogenated over 2 g. of 5% palladium-on carbon with hydrogen at 50 lbs. per sq. inch and at room temperature. The catalyst was separated by filtration and the cycloalkylacetonitrile was distilled.

*3-Methylcyclopentylacetonitrile.* Yield 97%, b.p. 79° at 10 mm., $n_D^{25}$ 1.4411.

*Anal.* Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 78.34; H, 10.86; N, 11.36.

*Cycloheptylacetonitrile.* Yield 88%, b.p. 102° at 10 mm., $n_D^{25}$ 1.4654.

*Anal.* Calcd. for $C_9H_{15}N$: N, 10.24. Found: N, 10.14.

*Acid hydrolysis of the cycloalkylacetonitriles and cycloalkenylacetonitriles.* A solution of 0.8 mole of the cycloalkyl acetonitrile or cycloalkenylacetonitrile in 200 ml. of dioxane and 400 ml. of coned. hydrochloric acid was boiled under reflux for 24–48 hr. The dioxane was distilled under reduced pressure and the organic layer was extracted into ether. The ether solution was extracted with 2% sodium hydroxide solution. Acidification of the basic aqueous layer yielded the carboxylic acid which was dried and distilled. The ether layer was evaporated and the residue was distilled to yield the lactones of the 1-cycloalkenylacetic acids.

*Cycloheptylacetic acid.* Yield 57%, b.p. 146–147° at 10 mm. (reported[8] b.p. 165° at 19 mm.).

*1-Cyclohexenylacetic acid.* Yield 66%, $n_D^{25}$ 1.4852, b.p. 150–155° at 13 mm. (reported[9] b.p. 145° at 17 mm.).

*1-Cyclopentenylacetic acid and 2-ketohexahydrocyclopenta[b]-furan.* Yield 41%, $n_D^{25}$ 1.4771. The distillate was considered to be a mixture of almost equal parts of 1-cyclopentenylacetic acid and the lactone 2-ketohexahydrocyclopenta[b]furan because of the presence of two equally intense carbonyl bands. The lactone carbonyl band was at 5.65 $\mu$ and the carboxylic carbonyl band was at 5.84 $\mu$. The carboxylic group was also in evidence by the carboxylic acid OH dimer bands in the 3.6–4.2 $\mu$ region. An intense C=C band is present at 6.05 $\mu$ and a lactone ester band at 8.1 $\mu$.

*Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.56; H, 7.98. Found: C, 66.10. H, 7.94.

Sixty-four grams of the mixture of carboxylic acid and lactone was allowed to stand with an excess of thionyl chloride. The mixture was distilled. After the excess thionyl chloride was collected, the carboxylic acid chloride believed to be 1-cyclopentenylacetyl chloride boiled at 88–100° at 10 mm.; yield 25.6 g. or 40%. The lactone boiled at 118–120° at 10 mm.; yield 35 g. or 55%. The lactone was insoluble in cold sodium hydroxide solution.

*3-Methylcyclopentylacetic acid.* Yield 58%, b.p. 120–124° at 10 mm., $n_D^{25}$ 1.4472.

*Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; O, 22.51. Found: C, 67.17; H, 9.38; O, 22.58.

*2-Ketooctahydrocyclohepta[b]furan.* Yield 70%, b.p. 146–150° at 10 mm.

*2-Keto-4- or 6α-methylhexahydrocyclopenta[b]furan.* Yield 74%, b.p. 111–112° at 10 mm., $n_D^{25}$ 1.4636.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.58; H, 8.47.

*5-Norbornylenylacetic acid.* A mixture of 17.2 g. (0.705 mole) of magnesium turnings, 80 ml. of dry ether, 10 g. of 5-norbornylenylmethyl bromide,[10] and a crystal of iodine was stirred in a three-necked flask fitted with a condenser. After the reaction started, 121.8 g. (0.705 mole total) of 5-norborenylenylmethyl bromide was diluted with 250 ml. of ether and added dropwise at a rate that maintained gentle refluxing. After complete addition, the mixture was refluxed for 1 hr. and then poured into a slurry of a large excess of Dry Ice in ether. The total mixture was then poured into ice and concentrated hydrochloric acid. The ether phase was separated and extracted with 500 ml. of 10% sodium hydroxide. The aqueous layer was cooled and acidified with concentrated hydrochloric acid. The liberated oil was extracted into ether, dried, filtered, and the ether evaporated.

(4) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, *Org. Syntheses*, **31**, 25 (1951).

(5) W. C. McCarthy and T. H. Brown, *J. Am. Pharm. Assoc.*, **43**, 661 (1954).

(6) E. Rohrmann, U.S. Patent 2,520,015 (*Chem. Abstr.*, **45**, 647h (1951).

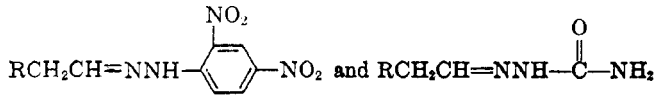
(7) R. D. Desai, *J. Chem. Soc.*, 1931, 1216.

(8) O. Wallach, *Ann.*, **353**, 284 (1907).

(9) J. Harding, W. N. Haworth, and W. H. Perkin, Jr., *J. Chem. Soc.*, **93**, 1959 (1908).

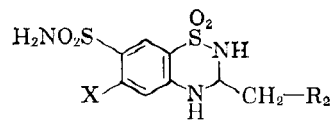
(10) K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

TABLE II




| R | Formula | M.P. | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|
| 2-Cyclopentenyl | $C_8H_{13}N_3O$ | 116–117 | 57.46 | 7.84 | 25.13 | 57.13 | 7.94 | 25.22 |
| 3-Cyclohexenyl | $C_9H_{15}N_3O$ | 142–144 | 59.64 | 8.34 | 23.19 | 59.80 | 8.62 | 23.01 |
| 3-Methylcyclopentyl | $C_9H_{17}N_3O$ | 126–127 | 58.98 | 9.35 | 22.93 | 59.05 | 9.46 | 23.02 |
| Cycloheptyl | $C_{10}H_{19}N_3O$ | 160–161 | 60.88 | 9.71 | 21.30 | 61.11 | 9.77 | 21.45 |
| 1-Methylcyclohexyl | $C_{10}H_{19}N_3O$ | 170–171 | 60.88 | 9.71 | 21.30 | 61.04 | 9.64 | 20.91 |
| 2-Cyclopentenyl | $C_{13}H_{14}N_4O_4$ | 98–99 | 53.79 | 4.86 | 19.29 | 53.79 | 4.84 | 19.36 |
| Cyclopentyl | $C_{13}H_{16}N_4O_4$ | 128–129 | 53.42 | 5.52 | 19.17 | 53.43 | 5.55 | 19.36 |
| 2-Cyclohexenyl | $C_{14}H_{16}N_4O_4$ | 97 | 55.25 | 5.30 | 18.41 | 55.60 | 5.35 | 18.37 |
| 3-Methylcyclopentyl | $C_{14}H_{18}N_4O_4$ | 91–92 | 54.89 | 5.92 | 18.29 | 54.73 | 5.65 | 18.20 |
| 5-Norbornylenyl | $C_{15}H_{16}N_4O_4$ | 124–125 | 56.95 | 5.09 | 17.71 | 56.58 | 5.30 | 17.56 |
| Cycloheptyl | $C_{15}H_{20}N_4O_4$ | 96–97 | 56.24 | 6.29 | 17.49 | 56.49 | 6.42 | 17.43 |

TABLE III




| $R_2$ | X | Formula | Yield, % | M.P., | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| 2-Cyclopentenyl | Cl | $C_{13}H_{16}ClN_3O_4S_2$ | 71 | 222 | 41.32 | 4.27 | 11.33 | 41.35 | 4.17 | 11.25 |
| Cyclopentyl | Cl | $C_{13}H_{18}ClN_3O_4S_2$ | 84 | 230 | 41.10 | 4.78 | 11.06 | 41.04 | 4.60 | 11.00 |
| Cyclopentyl | Br | $C_{13}H_{18}BrN_3O_4S_2$ | 80 | 228 | 36.84 | 4.24 | 9.93 | 36.80 | 4.27 | 10.19 |
| *n*-Hexyl | Cl | $C_{13}H_{20}ClN_3O_4S_2$ | 40 | 172[a] | | | 11.00 | | | 10.82 |
| 2-Cyclopentenyl | $CF_3$ | $C_{14}H_{16}F_3N_3O_4S_2$ | 70 | 148[a] | 40.87 | 3.92 | 10.21 | 40.15 | 4.41 | 10.18 |
| 2-Cyclohexenyl | Cl | $C_{14}H_{18}ClN_3O_4S_2$ | 85 | 221 | 42.92 | 4.63 | 10.72 | 43.10 | 4.70 | 10.37 |
| 2-Cyclohexenyl | Br | $C_{14}H_{18}BrN_3O_4S_2$ | 80 | 215 | | | 9.64 | | | 9.63 |
| 3-Cyclohexenyl | Cl | $C_{14}H_{18}ClN_3O_4S_2$ | 35 | 215 | 42.91 | 4.60 | | 43.18 | 4.66 | |
| 3-Cyclohexenyl | Br | $C_{14}H_{18}BrN_3O_4S_2$ | 32 | 202 | 38.54 | 4.16 | 9.64 | 38.74 | 4.31 | 9.63 |
| Cyclopentyl | $CF_3$ | $C_{14}H_{18}F_3N_3O_4S_2$ | 70 | 156[a] | 40.67 | 4.39 | 10.16 | 40.91 | 4.60 | 10.24 |
| 1-Cyclohexenyl | Cl | $C_{14}H_{18}ClN_3O_4S_2$ | 65 | 225 | 42.95 | 4.53 | 10.75 | 42.48 | 4.70 | 10.70 |
| 3-Methylcyclopentyl | Cl | $C_{14}H_{20}ClN_3O_4S_2$ | 80 | 198[a] | 42.75 | 5.12 | 10.69 | 42.23 | 5.29 | 10.74 |
| 3-Methylcyclopentyl | Br | $C_{14}H_{20}BrN_3O_4S_2$ | 80 | 100[a] | 38.32 | 4.59 | 9.61 | 38.21 | 4.68 | 9.70 |
| Cyclohexyl | Cl | $C_{14}H_{20}ClN_3O_4S_2$ | 85 | 232 | 42.75 | 5.12 | 10.71 | 42.49 | 5.13 | 10.80 |
| Cyclohexyl | Br | $C_{14}H_{20}BrN_3O_4S_2$ | 80 | 214 | 38.32 | 4.59 | 9.61 | 38.27 | 4.61 | 9.77 |
| 5-Norbornylenyl | Cl | $C_{15}H_{18}ClN_3O_4S_2$ | 40 | 210 | 45.38[b] | 5.37 | 9.34 | 45.33 | 5.27 | 9.78 |
| 2-Cyclohexenyl | $CF_3$ | $C_{15}H_{18}F_3N_3O_4S_2$ | 86 | 202 | 42.47 | 4.72 | 9.86 | 42.82 | 4.47 | 9.97 |
| 3-Methylcyclopentyl | $CF_3$ | $C_{16}H_{20}F_3N_3O_4S_2$ | 85 | 185[a] | 42.47 | 4.72 | 9.86 | 42.52 | 5.05 | 9.91 |
| Cycloheptyl | Cl | $C_{15}H_{22}ClN_3O_4S_2$ | 93 | 215 | | | 10.31 | | | 10.02 |
| Cycloheptyl | Br | $C_{15}H_{22}BrN_3O_4S_2$ | 76 | 214 | 39.82 | 4.92 | 9.28 | 40.19 | 5.08 | 9.12 |
| 1-Methylcyclohexyl | Cl | $C_{15}H_{22}ClN_3O_4S_2$ | 35 | 245 | 44.16 | 5.44 | 10.30 | 44.34 | 5.68 | 10.29 |
| 5-Norbornylenyl | $CF_3$ | $C_{16}H_{22}F_3N_3O_4S_2$ | 76 | 228 | 43.93 | 4.15 | 9.61 | 44.44 | 4.40 | 9.31 |
| Cycloheptyl | $CF_3$ | $C_{16}H_{22}F_3N_3O_4S_2$ | 60 | 178 | 44.45[b] | 5.82 | 8.67 | 44.43 | 5.09 | 8.89 |
| 1-Methylcyclohexyl | $CF_3$ | $C_{16}H_{22}F_3N_3O_4S_2$ | 32 | 190[a] | 43.52 | 5.02 | 9.52 | 43.77 | 5.13 | 9.82 |

[a] The compounds melting below 200° were shown, by elemental analysis, to be solvated and could not be dried free of solvent when heated at moderate temperatures in a vacuum. A flash drying technique was used whereby a sample was heated at 180° for 1–5 min. Reasonably good elemental analysis could be obtained after this drying procedure. [b] Values include one molecule of solvated ethanol.

The oil, 65.5 g., was distilled at 139° and 12 mm., $n_D^{25}$ 1.4878, yield 58.3 g. (55%).

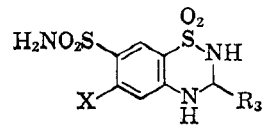
*Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95; O, 21.03. Found: C, 70.67; H, 7.92; O, 20.69.

*N-methyl-N-phenyl- and N,N-dimethylcycloalkyl- and cycloalkenylacetamides, Table I.* Cycloalkyl- and cycloalkenylacetic acids[11] were converted to acid chlorides with thionyl chloride. The amides were prepared in the usual way by treating the acid chlorides with *N*-methylaniline or *N,N*-dimethylamine and pyridine in benzene solution. The benzene solution was washed with water and dried over anhydrous magnesium sulfate. The benzene was removed under reduced pressure on the steam bath. The amides were distilled under reduced pressure.

*Reduction of the N-methylcycloalkyl- and N-methylcycloalkenylacetanilides.* Tetrahydrofuran was dried by distillation over calcium hydride. One mole of the *N*-methylcycloalkyl- or *N*-methylcycloalkenylacetanilide was dissolved in 220 ml. of dry tetrahydrofuran and added to a 3-l. three-

(11) See the preceding paper for the source of some of these acids.

TABLE IV



| $R_3$ | X | Formula | Yield, % | M.P. | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| 2,3-Dihydro-2-γ-pyranyl | Cl | $C_{12}H_{14}ClN_3O_5S_2$ | 30 | 235 | 37.94 | 3.72 | | 37.94 | 4.02 | |
| 5-Norbornylenyl | Cl | $C_{14}H_{16}ClN_3O_4S_2$ | 46 | 234 | 43.13 | 4.14 | 10.78 | 43.13 | 3.89 | 10.69 |
| 2-Norbornyl[a] | Cl | $C_{14}H_{18}ClN_3O_4S_2$ | 80 | 263 | 42.80 | 4.60 | 10.75 | 42.89 | 4.35 | 10.79 |
| 6-Methylcyclohexenyl | Cl | $C_{14}H_{18}ClN_3O_4S_2$ | 75 | 230 | 42.80 | 4.60 | 10.75 | 43.03 | 4.50 | 10.58 |
| 6-Methylcyclohexenyl | Br | $C_{14}H_{18}BrN_3O_4S_2$ | 78 | 230 | | | 9.64 | | | 9.45 |
| 6-Methyl-5-norbornylenyl | Cl | $C_{15}H_{18}ClN_3O_4S_2$ | 40 | 235 | 44.60 | 4.49 | 10.40 | 44.58 | 4.72 | 10.22 |

[a] This was prepared by the catalytic reduction of the above compound.

necked flask. The flask was fitted with a condenser, a 250-ml. dropping funnel, and a mechanical stirrer. Lithium aluminum hydride, 12.5 g. (0.33 mole), was crushed to a powder in a glass mortar. Caution was taken during this operation to prevent ignition of the hydride and 6.25-g. portions were crushed at one time. The powdered lithium aluminum hydride was immediately placed in a 500-ml. flask, slurried with 150–200 ml. of cold dry tetrahydrofuran, then cooled in ice. Small portions of the lithium aluminum hydride were added to the stirred solution of the *N*-methylacetanilide through the dropping funnel. The addition required 2 hr. The mixture was stirred overnight. During this time the ice in the bath was allowed to melt. The flask was again cooled in ice and 500 ml. of *6N* hydrochloric acid was added cautiously in small portions. Ether was added and the aldehyde was extracted, then washed with water until the wash water was neutral. The ether layer was dried over magnesium sulfate and filtered. The ether solution was then distilled. Ether and tetrahydrofuran distilled below 45° at 17 mm. and the aldehyde was collected above 45°. Semicarbazones and 2,4-dinitrophenylhydrazones were prepared of the aldehydes for their characterization, Table II. Unchanged *N*-methylanilides boiled at temperatures higher than the boiling points of the aldehydes. The yields reported in parentheses are based on the amount of anilide actually used in the reactions.

*2-Cyclopentenylacetaldehyde.* Yield 46.5% (75%), b.p. 53–56° at 12 mm., $n_D^{25}$ 1.4604.

*Cyclopentylacetaldehyde.* Yield 55% (95%), b.p. 53° at 12 mm., 156° at 760 mm.

*Cyclohexylacetaldehyde.* Yield 45% (78%), b.p. 68–70° at 15 mm., $n_D^{25}$ 1.4615.

*2-Cyclohexenylacetaldehyde.* Yield 33% (60%), b.p. 65° at 13 mm.

*3-Cyclohexenylacetaldehyde.* Yield 27% (60%), b.p. 87–127° at 10 mm.

*3-Methylcyclopentylacetaldehyde.* Yield 44% (53%), b.p. 63–66° at 12 mm., $n_D^{25}$ 1.4421.

*1-Methylcyclohexylacetaldehyde.* Yield 39% (55%), b.p. 82–85° at 11 mm., $n_D^{25}$ 1.4619.

*Cycloheptylacetaldehyde.* Yield 33% (56%), b.p. 98–103° at 19 mm., $n_D^{25}$ 1.4652.

*5-Norbornylenylacetaldehyde.* Yield 32% (92%), b.p. 76–78° at 8 mm., $n_D^{25}$ 1.4851.

*Reduction of N,N-dimethylcycloalkenylacetamides.* An ether solution of lithium diethoxyaluminum hydride (0.156 mole) was prepared from lithium aluminum hydride and ethyl acetate by the method of Brown and Tsukamoto.[12] This reagent was added over a period of 30 min. to a well stirred solution (0.26 mole) of the *N,N*-dimethylcycloalkenylacetamide in 200 ml. of ether at 0–5°. The mixture was then stirred at room temperature for 12 hr. and hydrolyzed with *2N* sulfuric acid at 0°. The aldehyde-ether solution was washed with water, dried over magnesium sulfate, and distilled under reduced pressure.

*2-Cyclopentenylacetaldehyde.* Yield 23%, b.p. 53° at 12 mm.

*1-Cyclohexenylacetaldehyde.* Yield 17%, b.p. 53–64° at 2.5–3.5 mm.

*3,4-Dihydro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides.* Tables III and IV. The following suspensions were prepared: One-tenth mole (28.5 g.) of 4-amino-6-chlorobenzene-1,3-disulfonamide in 400 ml. of warm 50% *6N* hydrochloric acid and ethanol, 0.1 mole (31.9 g.) of 4-amino-6-trifluoromethylbenzene-1,3-disulfonamide in 200 ml. of warm 50% *6N* hydrochloric acid and ethanol, and 0.1 mole (33 g.) of 4-amino-6-bromobenzene-1,3-disulfonamide in 300 ml. of warm 50% *6N* hydrochloric acid and ethanol. One-tenth mole of the appropriate aldehyde was added to each suspension and the mixture shaken for 0.5 hr. The mixtures were cooled in ice after standing at room temperature for 12 hr. The precipitated-product was collected and washed with water until it was free of mineral acid. If the product had not completely separated, water was added which caused further precipitation. The 3,4-dihydro - 3 - substituted 7 - sulfamoyl - 1,2,4 - benzothiadiazine 1,1-dioxides were dissolved in a minimum amount of warm alcohol and then diluted with water to incipient turbidity. The crystalline products were further purified by repeated crystallization from dilute alcohol.

*Sodium borohydride reduction.* To 75 ml. of dry tetrahydrofuran in a three-necked flask was added 0.1 mole of the 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide. See the preceding paper. The mixture was stirred and 1.5 g. (0.04 mole) of sodium borohydride was added portionwise. There was evolution of heat and the solids dissolved. Anhydrous aluminum trichloride, 1.5 g. or 0.015 mole, dissolved in 50 ml. of tetrahydrofuran, was added dropwise. After the evolution of the hydrogen was complete, the mixture was heated to boiling for 2 hr. and allowed to stand overnight. The cooled mixture was stirred and 15 ml. of water added dropwise, followed by addition of dilute acid. Solids were separated by filtration and the filtrate evaporated under reduced pressure to yield the product which was recrystallized from ethyl acetate–petroleum ether and then from dilute alcohol.

*6-Chloro-3-cyclopentylmethyl-3,4-dihydro-7-(N-methylsulfamoyl)-1,2,4-benzothiadiazine-1,1-dioxide.* Yield 12%, m.p. 174–175°.

*Anal.* Calcd. for $C_{14}H_{20}ClN_3O_4S_2$: C, 42.68; H, 5.12; N, 10.66. Found: C, 41.60; H, 5.28; N, 10.92.

6-Chloro-3-cyclohexylmethyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide was obtained in 60% yield and 6-chloro-3-cyclopentylmethyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide in 40% yield.

*Diuretic activity.* The saluretic and diuretic activities of the compounds listed in Tables III and IV were determined

(12) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, 81, 502 (1959).

by a modified method of Lipschitz.[13] They were found to be more active than the parent compound 6-chloro-3,4-dihydro - 7 - sulfamoyl - 1,2,4 - benzothiadiazine 1,1-dioxide. The most active compounds (200–300 times the parent compound) were similar in structure to the most active compounds listed in the preceding paper.

(13) W. L. Lipschitz, Z. Hadidian, and A. Kurpcsar, *J. Pharm. Exper. Therap.*, **79**, 97 (1943).

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[CONTRIBUTION FROM THE DEPARTMENT OF NUTRITION AND METABOLIC DISEASES, THE UPJOHN CO.]

# 8-Chloroalloxazine, A New Diuretic. Synthesis and Structure

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8-Chloroalloxazine, a new diuretic, can be obtained in good yield and purity by the condensation of alloxan with 4-chloro-2-aminoaniline (1,2-diamino-4-chlorobenzene) in strongly acidic aqueous solutions or in glacial acetic acid in the presence of boric acid. When the same condensation is carried out in weakly acidic aqueous solution or neutral solvents, 2-hydroxy-6-chloroquinoxaline-3-carboxyureide is the main or exclusive product. Evidence for the structure of these compounds is derived from degradation studies, physical properties, and a comparison of these with the products formed when alloxan and 1,2-diaminobenzene are condensed, the latter reaction giving well characterized compounds.

Diuretic activity of clinical significance is a pharmacodynamic property shown by a limited number of structures,[1] and the recent discovery of such activity in several new types of compounds, including sulfonamyl derivatives and carbonic anhydrase inhibitors,[2] has led to a renewed interest in this aspect of medicinal chemistry. Therefore, the finding by Graham[3] of diuretic activity in rats and dogs when a chloroalloxazine of unknown structure was administered orally seemed to be of sufficient importance to warrant expending considerable effort to determine the chemical nature of the compound responsible for the biological activity. In this paper are described the studies which established the structure of the diuretic and led to unequivocal methods for its preparation.

A compound designated as 7(8)-chloroalloxazine was one of a series of alloxazines and isoalloxazines prepared for the investigation of the possible antitumor activity of riboflavin inhibitors. This compound was prepared according to the method described by Wolf *et al.*,[4] which involves the condensation of alloxan and the appropriate ortho-phenylenediamine. The purity of the 7(8)-chloroalloxazine mentioned by Wolf *et al.* was never established but work presented here indicates the reaction of 4-chloro-2-aminoaniline (I) and alloxan (II) (*cf.* Fig. 1) leads to the formation either of 8-chloroalloxazine (III) or of 2-hydroxy-6-chloroquinoxaline-3-carboxyureide (IV) and that there is no evidence of the formation of 7-chloroalloxazine under any conditions studied by either Wolf *et al.* or us. 2-Hydroxy - 6 - chloroquinoxaline - 3 - carboxyureide (IV) has no diuretic activity, but its presence in some preparations for a time obscured the biological results.

The conditions leading to the formation of 8-chloroalloxazine alone involve the condensation of 4-chloro-2-aminoaniline (I) and alloxan (II) in glacial acetic acid in the presence of boric acid at room temperature or the condensation of these reactants in 1–5*N* hydrochloric acid with heat. If aqueous acetic acid is used even in the presence of boric acid, 2-hydroxy-6-chloroquinoxaline-3-carboxyureide (IV) is formed. If boric acid is eliminated from the glacial acetic acid reaction medium or is present below 0.03 molar equivalents, IV is formed along with III. Similarly, if the hydrochloric acid medium is at an acidity lower than 1*N*, IV is formed as an impurity along with III. It is therefore apparent that 8-chloroalloxazine (III) is formed only under limited conditions of reaction, these being the subject matter of much of this presentation.

When I and II are condensed in neutral solvents, such as ethanol or cellosolve, or neutral or slightly acidic aqueous media, only IV is formed. This is in harmony with the findings of King and Clark-Lewis[5] and Barlow, Ing, and Lewis,[6] who showed that the reaction of alloxan and *o*-phenylenediamine in neutral solutions yielded 2-hydroxyquinoxaline-3-

(1) For a review of the mercurial, xanthine, and isocytosine diuretics, the reader is referred to R. F. Pitts, *The Physiological Basis of Diuretic Therapy*, Charles C Thomas, Springfield, Ill., 1959.

(2) Carroll A. Handley and John H. Moyer, *The Pharmacology and Clinical Use of Diuretics*, Charles C Thomas, Springfield, Ill., 1959.

(3) B. E. Graham, unpublished communication.

(4) F. J. Wolf, R. H. Beutel, and J. R. Stevens, *J. Am. Chem. Soc.*, **70**, 2572 (1948).

(5) F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.*, 3379 (1951).

(6) R. B. Barlow, H. R. Ing, and I. M. Lewis, *J. Chem. Soc.*, 3242 (1951).