# New Compounds: 4-Substituted 5,6-Dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-ones, Potential Psychopharmacological Drugs

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**Abstract** □ The synthesis of 16 derivatives of a 1,3,4-oxadiazine, each of which may be envisioned as forming a tricyclic structure, was carried out by 4-alkylation and further reaction with a secondary amine. The compounds are proposed as potential psychopharmacological drugs.

**Keyphrases** □ 5,6-Dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-ones, 4-substituted—synthesized as potential psychopharmacological drugs □ Psychopharmacological agents, potential—synthesis of 4-substituted 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-ones □ Oxadiazines—synthesis of 4-substituted 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-ones

As a part of a program of synthesis of potential new psychopharmacological drugs derived from little explored heterocycles[1], several derivatives were obtained from a previously described compound, 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-one (4). An outstanding feature of these oxadiazines is their potential ability to form a tricyclic plane structure due to the ease with which a stable hydrogen bond may form between the *o*-phenolic group of the aromatic substitution on carbon 2 and the position 3 nitrogen, in effect producing a cryptophenol.

The *N*-4-alkylations involved two different approaches: direct alkylation, and a two-step process consisting of direct alkylation to yield an $\alpha$- or $\beta$-chloroalkyl derivative followed by treatment of the 4-chloroalkyloxadiazine with a secondary amine.

## EXPERIMENTAL[2]

**5,6-Dihydro-2-*o*-hydroxyphenyl-4-(2-chloroethyl)-4*H*-1,3,4-oxadiazine-5-one (III)**—A suspension of 0.01 mole (1.92 g) of 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-one in 35 ml of acetone was dissolved by adding, with stirring, 3.5 ml of 10% sodium hydroxide. After a few minutes the sodium salt crystallized; 0.026 mole (2.2 ml) of 1-bromo-2-chloroethane was then added and the mixture was refluxed for 2 hr. On standing overnight, the product crystallized (Table I).

**5,6-Dihydro-2-*o*-hydroxyphenyl-4-(3-chloropropyl)-4*H*-1,3,4-oxadiazine-5-one (IV)**—This compound was obtained by using the procedure for III with 1-bromo-3-chloropropane (Table I).

**4-Alkyl Oxadiazines: General Procedure**—*Method A*—To a suspension of 0.55 g of sodium methoxide in 35 ml of acetone was added, with stirring, 0.01 mole of 5,6-dihydro-2-*o*-hydroxyphenyl-

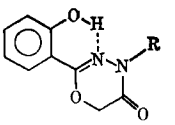


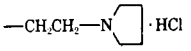
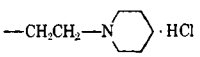
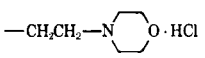
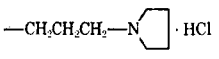
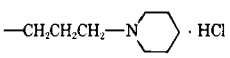
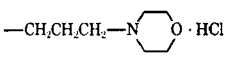
**Table I—Physical Constants** of Compounds I–XVI

| Compound | R | Method | Melting Point | Yield, % | Crystallization Solvent | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|
| I | $-CH_2CH_3$ | A | 78° | 75 | Methanol | C 60.00<br>H 5.40<br>N 12.73 | 59.92<br>5.38<br>12.70 |
| II | $-CH_2CH_2CH_3$ | A | 93° | 67 | Ethanol–water | C 61.53<br>H 5.98<br>N 11.96 | 61.50<br>5.93<br>11.95 |
| III | $-CH_2CH_2Cl$ | — | 164–165° | 63 | Dioxane | C 51.86<br>H 4.32<br>N 11.00 | 52.00<br>4.40<br>10.85 |
| IV | $-CH_2CH_2CH_2Cl$ | — | 168–169° | 74.6 | Dioxane | C 53.63<br>H 4.84<br>N 10.42 | 53.50<br>4.78<br>10.39 |
| V | $-CH_2-C_6H_5$ | A | 115° | 62 | Ethanol–water | C 68.08<br>H 4.96<br>N 9.92 | 68.00<br>4.99<br>9.89 |
| VI | $-CH_2CH_2O-C_6H_5$ | A | 110° | 50 | Cyclohexane–ethanol | C 65.38<br>H 5.13<br>N 8.97 | 65.35<br>5.15<br>8.96 |
| VII | $-CH_2CH_2O-C_6H_4-Cl$ | A | 133–139° | 59 | Ethanol | C 58.87<br>H 4.32<br>N 8.08 | 58.85<br>4.40<br>7.98 |
| VIII | $-CH_2CH_2O-C_6H_4-CH_3$ | A | 102–109° | 60 | Methanol | C 66.25<br>H 5.52<br>N 8.58 | 66.21<br>5.49<br>8.55 |

[1] Little information is available about 1,3,4-oxadiazines with pharmacological activity (1-3), and nothing is available concerning the corresponding 5-ones.

[2] Melting points (Buchi apparatus) are uncorrected; IR spectra recorded on Perkin-Elmer 137B Infracord; spectral data consistent with structure assigned; OH band, 3000 $cm^{-1}$; C=O, 1670 $cm^{-1}$ (potassium bromide).

**Table I**—(*Continued*)

| Compound | R | Method | Melting Point | Yield, % | Crystallization Solvent | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|---|
| IX | $-CH_2CH_2-N(CH_3)_2 \cdot HCl$ | B | 196° | 54 | Methanol–benzene | C 52.08<br>H 6.01<br>N 14.02 | 51.98<br>6.12<br>13.97 |
| X | $-CH_2CH_2-N(C_2H_5)_2 \cdot HCl$ | B | 199° | 58 | Methanol | C 54.96<br>H 6.71<br>N 12.82 | 55.05<br>6.75<br>13.00 |
| XI |  | B | 205–206° | 35 | Methanol–benzene | C 55.29<br>H 6.14<br>N 12.90 | 55.18<br>6.16<br>12.82 |
| XII |  | B | 231–232° | 79.4 | Ethanol | C 56.55<br>H 6.48<br>N 12.37 | 56.47<br>6.55<br>12.26 |
| XIII |  | B | 256–258° | 60 | Methanol–benzene | C 52.70<br>H 5.85<br>N 12.30 | 52.72<br>6.01<br>12.42 |
| XIV |  | B | 177–178° | 50.3 | Methanol | C 56.55<br>H 6.48<br>N 12.37 | 56.65<br>6.50<br>12.28 |
| XV |  | B | 204–205° | 35 | Methanol | C 59.38<br>H 6.98<br>N 9.31 | 59.29<br>7.00<br>9.30 |
| XVI |  | B | 223–224° | 70.6 | Methanol | C 54.01<br>H 6.19<br>N 11.81 | 53.96<br>6.30<br>11.90 |

4*H*-1,3,4-oxadiazine-5-one. After a few minutes the sodium salt crystallized. Then 0.02 mole of the appropriate bromo derivative was added, and the mixture was refluxed for 5 hr and filtered. The solvent was evaporated *in vacuo* and the solid residue was crystallized from an appropriate solvent (Table I).

*Method B*—A mixture of 0.01 mole of III or IV and 0.06 mole of the corresponding secondary amine was heated at 80° in an oil bath for 6 hr and filtered, and the excess base was evaporated *in vacuo* at 80°. The residue was dissolved in benzene and the hydrochloride was precipitated by adding a solution of anhydrous hydrochloric acid in ether. It was recrystallized from an appropriate solvent (Table I).

## REFERENCES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