

Intramolecular Cyclization of *N'*-Chloroacetylsalicylhydrazide

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Treatment of *N'*-chloroacetylsalicylhydrazide (I) with sodium hydroxide in dimethylformamide produces an intramolecular cyclization. Of all theoretically possible reactions, only one proceeds to give 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazin-5-one (II). No formation of the 1,4,5-benzoxadiazocin-3,6-dione (III) is detected. The structure of II, as well as of its acetylation, methylation and hydrolysis derivatives are discussed.

Due to our interest in the synthesis of new medium-sized heterocycles related to hydrazine as potential psychopharmacological drugs with monoaminooxidase inhibitory properties, we tried to synthesize the 1,4,5-benzoxadiazocin-3,6-dione (III) from *N'*-chloroacetylsalicylhydrazide (I) (Scheme 1).

By the action of one equivalent of sodium hydroxide in dimethylformamide solution on I, a cyclized compound was obtained. Although a phenolic group was present, the reaction did not proceed to phenol alkylation; instead the enolic form of the hydrazide produced 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazin-5-one (II) in good yield

SCHEME 1

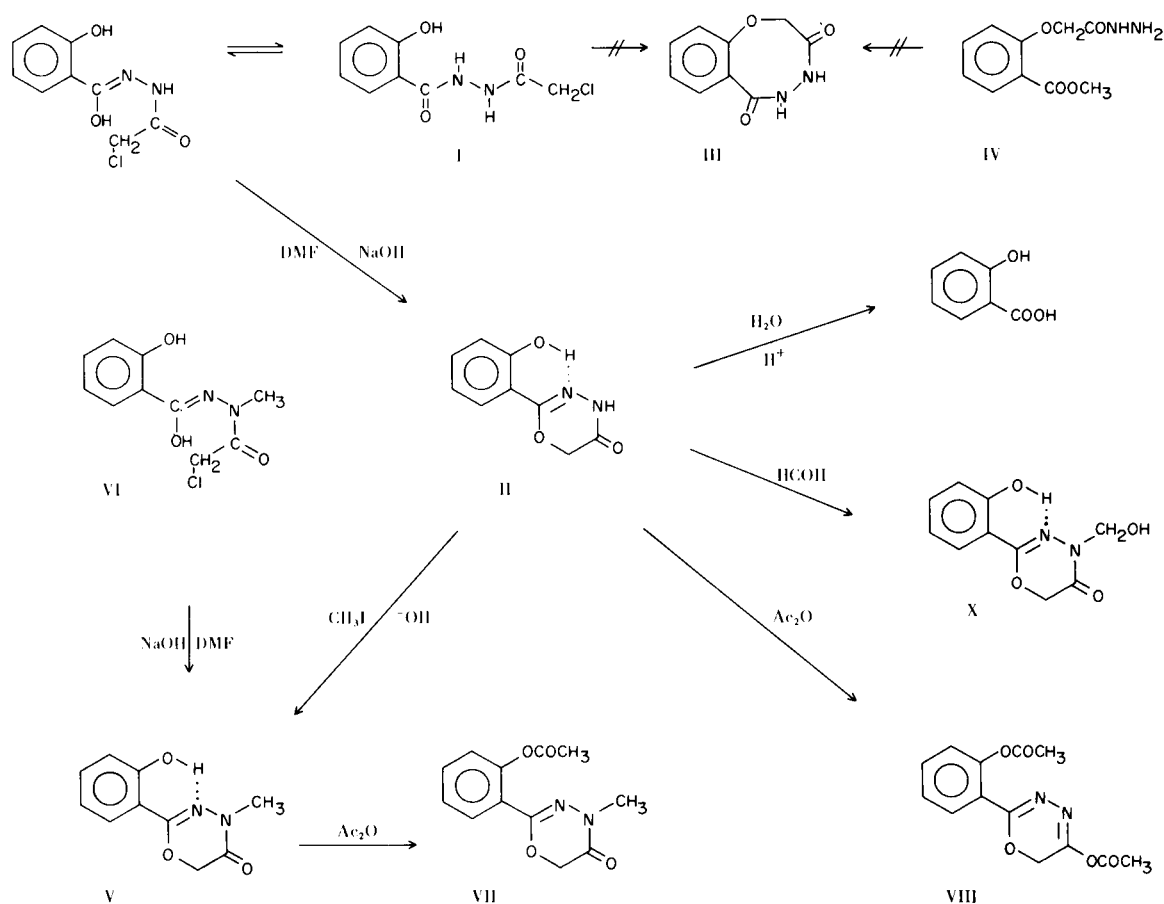
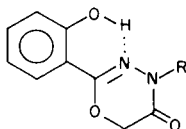


TABLE I

5,6-Dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazin-5-ones

Compound	R	Yield %	M.p. °C	Recrystallization Solvent	Molecular Formula		C	H	N
II	H	69	199-200	Ethanol-water	C ₉ H ₈ N ₂ O ₃	Calcd.:	56.2	4.17	14.6
						Found:	56.5	4.43	14.5
V	CH ₃	58	164-165	Ethanol-water	C ₁₀ H ₁₀ N ₂ O ₃	Calcd.:	58.3	4.85	13.6
						Found:	58.4	4.97	13.6
IX	C ₆ H ₅	62	158-159	Benzene-ligroin	C ₁₅ H ₁₂ N ₂ O ₃	Calcd.:	67.2	4.48	10.4
						Found:	67.4	4.61	10.6
X	CH ₂ OH	58	170-171	Water-ethanol	C ₁₀ H ₁₀ N ₂ O ₄	Calcd.:	54.1	4.51	12.6
						Found:	54.4	4.67	12.7

TABLE II

Nmr Data

Compound	Types of Hydrogen and Chemical Shifts; δ (ppm)				
	NH	OH	ArH	CH ₂	CH ³
II	11.4 (s)	11.6 (s)	6.8-7.8 (m)	4.9 (s)	---
V	---	10.1 (s)	6.8-7.8 (m)	4.8 (s)	3.4 (s)

and low resin formation.

This reaction followed a course similar to that described by Van Alphen (2) for several *N'*-chloroacetylhydrazides when heated with sodium carbonate in acetone in a closed vessel and related to that described by Field *et al.* (3).

An attempt to obtain III by intramolecular hydrazinolysis of the ester IV failed and starting material was recovered (Scheme 1).

The structure of compound II was established by analysis, molecular weight (Rast), nmr spectra (Table II), infrared spectra (Table III) and by acid hydrolysis which yielded quantitatively salicylic acid. Employing the same ring closure method, the analogous oxadiazine, 5,6-dihydro-2-phenyl-4*H*-1,3,4-oxadiazin-5-one, without the phenolic group, was obtained, identical to a sample prepared according to the method of Van Alphen (2c), thus confirming the proposed reaction course.

Compound II, which exhibited, as expected, two active hydrogen atoms by the Zerewitinoff's test, was soluble in an aqueous alkali, released a single acid hydrogen by potentiometric titration, gave no color when treated with

ferric chloride and when alkylated with methyl iodide in base, yielded exclusively a monomethyl derivative (V); all attempts of additional methylation, even with diazomethane in ether, failed. The compound V was an *N*-methyl derivative; it showed an OH band at 3000 cm⁻¹ in the ir spectra, was insoluble in alkalis and did not release an acidic hydrogen that could be potentiometrically titrated. Because of these features in II and V, we concluded that the phenolic group behaved like a cryptophenol (4) due to the formation of a stable hydrogen bond with the 3-nitrogen of the ring; this assumption was supported by the large chemical shift of the phenol-OH proton in the nmr spectra ($\delta = 11.6$).

The structure of compound V was confirmed by a second synthesis, when it was obtained from *N'*-methyl-*N'*-chloroacetylsalicylhydrazide (VI) (see Experimental).

The infrared spectra of II and V show a strong carbonyl band at 1670 cm⁻¹ and the group O=C=N at 1630 cm⁻¹, with the regular features of these oxadiazines as Bird (5) describes in a similar oxadiazine.

Acetylation of V with acetic anhydride proceeded slowly, giving VII; acetylation of II formed a diacetyl derivative (VIII), in which the carbonyl band of the ring at 1670 cm⁻¹ was not present indicating *O*-acetylation of the enolic form (Table III).

The attempts to prepare Mannich bases from II and V produced only the 4-hydroxymethyl derivative of II (IX); this result confirmed that the 4-nitrogen is the carrier of the acid hydrogen able to be potentiometrically titrated and is the one substituted by methylation.

TABLE III

Infrared Spectral Data of 1,3,4-Oxadiazines

Compound	C=O (ring)	C=O (acetyl)	O-H	N-H	C-O-C	O-C-N
II	1670 (s)	---	3000 (m)	3190 (m)	1090 (m)	1630 (s)
V	1670 (s)	---	3000 (m)	---	1090 (m)	1630 (s)
VII	1670 (s)	1750 (m)	---	---	1080 (m)	1630 (s)
VIII	---	1750 (s)	---	---	1080 (m)	1630 (s)
IX	1690 (s)	---	3120 (m)	---	1090 (m)	1630 (s)
X	1650 (s)	---	3400 (m)	---	1090 (m)	1630 (s)
XII	1650 (s)	---	---	3190 (m)	1090 (m)	1630 (s)

In addition, 5,6-dihydro-4-phenyl-4*H*-1,3,4-oxadiazin-5-one (IX), was obtained by the general procedure from *N'*-phenyl-*N'*-chloroacetylsalicylhydrazide (XI).

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 (potassium bromide). The nmr spectra were obtained with a Varian A-60 Spectrometer (in dimethyl sulfoxide- D_6) using tetramethylsilane as an internal standard. The Zerewitinoff test was applied to determine active hydrogens using methyl-magnesium iodide in toluene. The potentiometric titrations with 0.1 *N* sodium hydroxide were carried out in alcoholic solution with a Beckman Zeromatic II potentiometer.

N'-Chloroacetylsalicylhydrazide (I).

A mixture of 10 g. of salicylhydrazide, 8.5 g. of chloroacetyl chloride and 40 ml. of dry dioxane was refluxed for 2 hours. After cooling, the crystals which separated were collected by filtration and were recrystallized from dioxane to give 13 g. (90%) of I, as colorless needles, m.p. 206-207°.

Anal. Calcd. for $C_9H_9ClN_2O_3$: C, 47.3; H, 3.94; N, 12.3. Found: C, 47.5; H, 4.07; N, 12.3.

5,6-Dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazin-5-one (II) and the 4-Substituted Derivatives. General Procedure.

A mixture of 2 g. of *N'*-chloroacetylsalicylhydrazide (or an *N'*-substituted-*N'*-chloroacetylsalicylhydrazide), 0.4 g. of sodium hydroxide and 25 ml. of dimethylformamide was heated at 130° in an oil bath for 2 hours with stirring and filtered. The solvent was evaporated *in vacuo* to give a dark brown solid residue, which was recrystallized from ethanol-water to afford 1.2 g. of white needles (see Table I).

5,6-Dihydro-2-*o*-hydroxyphenyl-4-methyl-4*H*-1,3,4-oxadiazin-5-one (V)

This product was obtained by the general procedure, from 2.1 g. of VI; the reaction afforded 1.0 g. of white needles (see Table I).

5,6-Dihydro-2-*O*-hydroxyphenyl-4-phenyl-4*H*-1,3,4-oxadiazin-5-one (IX).

This compound was obtained by the usual procedure from 2.6 g. of XI as white flakes (1.1 g.) (see Table I).

5,6-Dihydro-2-phenyl-4*H*-1,3,4-oxadiazin-5-one (XII).

This compound was obtained by the general procedure from 3.5 g. of *N'*-chloroacetylbenzoylhydrazide (2c), to yield 1.5 g. (51%) of XII; recrystallization from benzene-chloroform afforded white needles; m.p. and mixed m.p. with a sample obtained by the Van Alphen's method (2c) were identical, 161°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.3; H, 4.54; N, 15.9. Found: C, 61.1; H, 4.50; N, 15.7.

N'-Methylsalicylhydrazide.

A mixture of 30 g. of methyl salicylate, 15 g. of methylhydrazine and 30 ml. of ethanol was refluxed for 6 hours; solvent and excess ester were evaporated *in vacuo* and the solid residue was recrystallized from ethyl acetate-ligroin, giving 22 g. (67%) of white flakes, m.p. 128-129°. This compound did not form hydrazones with aldehydes.

Anal. Calcd. for $C_8H_{10}N_2O_2$: N, 16.9. Found: N, 16.7.

N'-methyl-*N'*-chloroacetylsalicylhydrazide (VI).

This compound was obtained by the same procedure used to obtain I, from 10.2 g. of *N'*-methylsalicylhydrazide; recrystallization from dioxane gave 12.5 g. (87%) of VI, white prisms, m.p. 182-183°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3$: C, 49.4; H, 4.53; N, 11.5. Found: C, 49.3; H, 4.58; N, 11.6.

N'-Phenyl-*N'*-chloroacetylsalicylhydrazide (XI).

A mixture of 5.2 g. of *N'*-phenylsalicylhydrazide (6), 3.8 g. of chloroacetyl chloride in 20 ml. of dioxane was heated on a boiling water bath for 3 hours, cooled, and poured into 50 ml. of water and stirred for 20 minutes; the oil which solidified upon standing, was triturated with water, filtered, dried at 50° and recrystallized from benzene-ligroin to afford 6.1 g. (91%) of white flakes, m.p. 164-165°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_3$: C, 59.1; H, 4.27; N, 9.19. Found: C, 59.3; H, 4.28; N, 9.14.

Ethyl *o*-(Carbomethoxy)phenoxyacetate.

Ten g. of ethyl chloroacetate, 14 g. of sodium iodide and 50 ml. of dry acetone was refluxed 1 hour with stirring, cooled and filtered; the filtrate was added to a suspension of 24.8 g. of sodium methyl salicylate in 50 ml. of 2-propanol and refluxed with stirring for 3 hours; after cooling and filtering, the solution was evaporated in a boiling water bath and the residual oil was

distilled at 155-160° (3.4 mm) yielding 8.5 g. (25%) of a colorless oil.

Anal. Calcd. for C₁₂H₁₄O₅: C, 60.5; H, 5.92. Found: C, 60.7; H, 5.98.

o-(Carbomethoxy)phenoxyacetic Acid Hydrazide (IV).

A mixture of 2.4 g. of ethyl *o*-(carbomethoxy)phenoxyacetate, 0.6 g. of hydrazine hydrate and 15 ml. of 2-propanol was refluxed 4 hours. Cooling caused white needles to crystallize, m.p. 124-125°.

Anal. Calcd. for C₁₀H₁₂N₂O₄: C, 53.6; H, 5.36; N, 12.5. Found: C, 53.8; H, 5.36; N, 12.6.

An Attempt to Obtain III from IV.

A mixture of 1.0 g. of IV and 10 ml. of pyridine was refluxed 8 hours, excess pyridine was evaporated *in vacuo* to dryness and the solid residue was recrystallized from 2-propanol to give 0.9 g. of the starting material, m.p. and mixed m.p. with an authentic sample were identical.

5,6-Dihydro-2-*o*-acetoxyphenyl-4-methyl-4*H*-1,3,4-oxadiazin-5-one (VII).

A mixture of 2.0 g. of V, 25 ml. of acetic anhydride and 0.05 g. of anhydrous sodium acetate was refluxed 8 hours. Excess anhydride was evaporated *in vacuo* to dryness and the solid residue was recrystallized from benzene-ligroin giving 1.4 g. (58%) of colorless prisms VII, m.p. 118-119°.

Anal. Calcd. for C₁₂H₁₂N₂O₄: C, 57.8; H, 4.83; N, 11.3. Found: C, 57.8; H, 4.88; N, 11.2.

6-Hydro-2-*o*-acetoxyphenyl-5-acetoxy-1,3,4-oxadiazine (VIII).

A mixture of 1.5 g. of II and 10 ml. of acetic anhydride was refluxed for 6 hours. On cooling there crystallized 1.6 g. (74%) of VIII; white flakes; recrystallized from acetic acid; m.p. 142-143°.

Anal. Calcd. for C₁₃H₁₂N₂O₅: C, 56.5; H, 4.38; N, 10.1. Found: C, 57.1; H, 4.32; N, 9.98.

5,6-Dihydro-2-*o*-hydroxyphenyl-4-methyl-4*H*-1,3,4-oxadiazin-5-one (V) from II.

A suspension of 1.8 g. of II in 40 ml. of acetone was dissolved by adding with stirring 10 ml. of 4% sodium hydroxide. After a few minutes the sodium salt crystallized; 2.7 g. of methyl iodide was then added and the mixture was stirred for 3 hours at room temperature and excess acetone (25 ml.) was evaporated on a steam bath. Cooling and filtering gave 1.7 g. (83%) of V, m.p. 163-164°. Recrystallization from ethanol-water did not raise the m.p. This compound was identical to an analytical sample of V in mixed m.p. and ir spectra.

Hydrolysis of II.

(a) Acid Hydrolysis.

A mixture of 0.5 g. of II and 20 ml. of hydrochloric acid was refluxed for 5 hours. Cooling and filtering gave 0.35 g. of white needles, m.p. 158°, identified as salicylic acid by mixed m.p. with an authentic sample.

(b) Alkaline Hydrolysis.

A mixture of 1 g. of II and 20 ml. of 20% sodium hydroxide was refluxed for 5 hours. After neutralization with hydrochloric acid the hot solution was filtered giving 0.40 g. of a solid; recrystallized from ethanol-water, it was identified with the starting material by mixed m.p. and ir spectra. The aqueous filtrate was evaporated *in vacuo* to dryness and the residue was crystallized from water to afford 0.25 g. of salicylic acid, m.p. 158° identified by mixed m.p.

5,6-Dihydro-2-*o*-hydroxyphenyl-4-hydroxymethyl-4*H*-1,3,4-oxadiazin-5-one (X).

A mixture of 1.0 g. of II and 15 ml. of 40% formol was heated on a steam bath for 2 hours and filtered; upon cooling 0.7 g. of white flakes was obtained (see Table I).

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