Synthesis and Acylating Properties of 4,5-Dihydro-6*H*-1,3,4-oxadiazin-6-ones [1]

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Received November 12, 1982

Cyclization of α-acylhydrazinoacids with dicyclohexylcarbodiimide or with acetic anhydride allows an easy entry to the little known class of 4,5-dihydro-6*H*-1,3,4-oxadiazin-6-ones. Such compounds maintain the optical activity of the starting hydrazino acids and may be exploited as useful acylating agents.

J. Heterocyclic Chem., **20**, 979 (1983).

A limited number of 4,5-dihydro-6*H*-1,3,4-oxadiazin-6-ones have been reported about ten years ago by Russian Authors [2] who prepared 5-alkylidene derivatives by cyclization of acylhydrazinomaleic acids. Freeman and coworkers obtained some 4-unsubstituted compounds by reduction of 1,3,4-oxadiazin-6-one 4-oxides which were prepared by oxidation of 1,4-dihydroxypyrazoles with peracids [3]. More recently, the synthesis of 6,6-dialkoxy-5,6-dihydrooxadiazines (acetals of oxadiazinones) by reaction of 1,1-dialkoxyethylenes with ethyl benzoylazocarboxylate was reported [4].

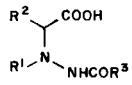
Because of our interest in the field of α-hydrazinoacids derivatives [5,6] we thought it worthwhile to achieve a general synthesis of 4,5-dihydro-6*H*-1,3,4-oxadiazin-6-ones (III) (Scheme I) which could be useful intermediates in the preparation of α-hydrazinoacyl derivatives protected at the hydrazino group. These heterocycles, in fact, may be considered aza homologues of azlactones which are well known acylating agents [7]. Apart from IIa, obtained by reduction of 2-(2-benzoylhydrazono)propionic acid with sodium amalgam, α-(2-acylhydrazino)acids IIb-e (Table 1) were prepared, in a general way, by acylation of α-hydrazinoacetic acids I with the appropriate anhydride.

Compounds IIa-e were cyclized to 4,5-dihydro-6*H*-1,3,4-oxadiazin-6-ones IIIa-f (Table 2) with dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (method A) or with acetic anhydride (method B). In the case of IIe (R^1 = H) method B afforded the 4-acetylated compound IIIf. Compounds substituted in position 2 with a methyl group (*e.g.*, IIIc) may be obtained directly from α-hydrazinoacids I by accomplishing both acetylation and cyclization with acetic anhydride in one step. Compound IIIe was also obtained in the racemic form following a different synthetic path: reaction of phenylglyoxylic acid with benzoylhydrazine gave *(Z)*-α-benzoylhydrazonophenylacetic acid (IV) whose configuration, so far undetermined [8,9], has been assigned on the basis of the chemical shift of NH proton (δ = 12.50 ppm) [10]. Compound IV was cyclized with DCC according to the method of Steglich *et al.* [9] to give 2,5-diphenyl-6*H*-1,3,4-oxadiazin-6-one (V) which afforded IIIe by reduction with zinc dust in acetic acid. The crude compounds III were purified by crystallization from 2-propanol or by chromatography over freshly activated silica gel to avoid hydrolytic cleavage.

Unlike analogues azlactones [7], compounds III may be obtained from optically active hydrazinoacids without

Table 1

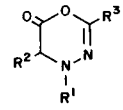
α-Acylhydrazinoacetic Acids II



Compound No.	R^1	R^2	R^3	Configuration	Yield (%)	Mp °C	$[\alpha]_D^{20}$, °, c = 1, 0.1 *N* sodium hydroxide	Molecular Formula	Analysis, % Calcd. C	H	N	Found C	H	N
IIa	H	CH_3	C_6H_5	RS	48	131-133	—	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46	57.32	5.69	13.39
IIb	CH_3	C_6H_5	H	R	28	129-131	−104.8	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46	57.47	5.71	13.34
IIc	CH_3	C_6H_5	CH_3	R	36	173-174 dec	−84.6	$C_{11}H_{14}N_2O_3$	59.45	6.35	12.60	59.68	6.30	12.77
IId	C_6H_5	C_6H_5	H	RS	52	153-155 dec	—	$C_{15}H_{14}N_2O_3$	66.65	5.22	10.37	66.50	5.13	10.41
IIe	H	C_6H_5	C_6H_5	R	72	168-169	−106.3	$C_{15}H_{14}N_2O_3$	66.65	5.22	10.37	66.81	5.27	10.36

Table 2

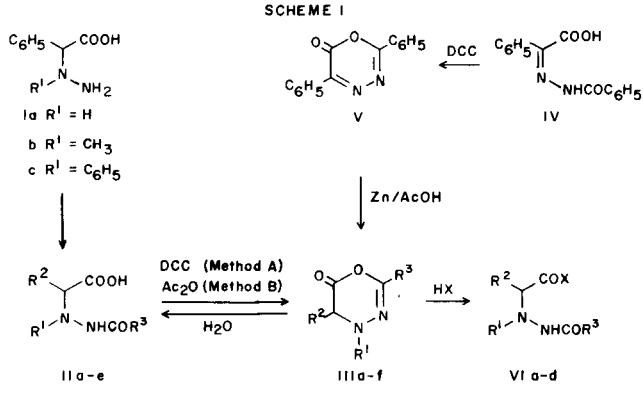
4,5-Dihydro-6*H*-1,3,4-oxadiazin-6-ones III



Compound No.	R^1	R^2	R^3	Yield % (Method)	Mp °C (a)	Configuration	$[\alpha]_D^{20}$, ° (c)	(d)	IR (b) C=O cm^{-1}	Molecular Formula	Analysis, % Calcd. C	H	N	Found C	H	N
IIIa	H	CH_3	C_6H_5	60 (A)	121-123	RS	—	—	1790	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	62.98	5.35	14.82
IIIb	CH_3	C_6H_5	H	74 (A) 66 (B)	74-75 (e)	R	−87.1	−106.4	1800	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	63.42	5.37	14.91
IIIc	CH_3	C_6H_5	CH_3	54 (A) 88 (f)	70-71	R	−105.8	−90.3	1790	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.82	6.02	13.66
IIId	C_6H_5	C_6H_5	H	79 (B)	146-148	RS	—	—	1795	$C_{15}H_{12}N_2O_2$	71.41	4.80	11.11	71.28	4.91	11.21
IIIe	H	C_6H_5	C_6H_5	20 (A) 55 (g)	143-145 159-161	R RS	+87.5 —	−101.3 —	1800 1800	$C_{15}H_{12}N_2O_2$	71.41	4.80	11.11	71.56	4.75	11.45
IIIf	CH_3CO	C_6H_5	C_6H_5	9 (B)	148-150	R	−299.9	—	1790	$C_{17}H_{14}N_2O_3$	69.37	4.80	9.52	69.52	4.85	9.45

(a) All the compounds, except IIIb, were crystallized from 2-propanol. (b) Spectra were recorded as oil mull. (c) c = 1 in chloroform. (d) A suspension of III (c = 0.5) in 0.1 *N* sodium hydroxide was stirred into solution before measuring the optical activity. (e) Chromatographed over freshly activated silica gel using hexane-ethyl acetate 7:3 as eluent. (f) By treatment of Ib with acetic anhydride: see experimental. (g) See experimental.

SCHEME I



racemization of the α-carbon atom; in fact alkaline hydrolysis gives back the acids II with unchanged optical activity.

Dihydrooxadiazinones III react smoothly with amines and hydrazines and more slowly with alcohols to give the amides, hydrazides and esters VIa-c (Table 3), which maintain the optical purity of the starting compounds. This property may be exploited for the preparation of β-lactam antibiotics as shown by the easy acylation of 7-aminocephalosporanic acid (7-ACA) *t*-butyl ester with IIIc to give the corresponding cephalosporin VId (Table 3) in fair yield.

EXPERIMENTAL

Melting points were determined using a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 157 spectrophotometer. The nmr spectra were determined with a Perkin-Elmer R 12B spectrometer, chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained by direct introduction on a Varian Mat 112 mass-spectrometer (electron energy 70 eV, emission, 1.5 mA). Omitted spectra were consistent with the assigned structure. Activated silica gel was prepared by stripping it with cyclohexane in a Dean-Stark apparatus.

α-Hydrazinoacetic Acids Ia-c.

Compounds Ia, b were obtained as previously reported [5].

(RS)-α-(1-Phenylhydrazino)phenylacetic Acid (Ic) Hydrochloride.

Phenylhydrazine (50.3 g, 0.465 mole) was added portionwise in an ice-cold solution of sodium *(RS)*-α-bromophenylacetate (110.7 g, 0.465 mole) in water (1 ℓ) and the mixture was stirred at room temperature for 3 hours. Sodium hydroxide (1*N*) was added to bring the *p*H to about 10 and the solution was washed with ethyl ether. The aqueous phase was then cooled to 0° and slowly acidified with dilute hydrochloric acid to *p*H 4.5. The solution was extracted with ethyl ether, the organic phase was dried with sodium sulfate and treated with hydrogen chloride in ethyl ether to precipitate 95.8 g (74%) of Ic as the hydrochloride, mp 160-161°; ir (oil mull): 2850-2500 (NH^+), 1730 cm^{-1} (C=O).

Anal. Calcd. for $C_{14}H_{14}N_2O_2 \cdot HCl$: Cl, 12.72; N, 10.05. Found: Cl, 12.74; N, 9.89.

α-Acylhydrazinoacetic Acids IIa-c (Table 1).

(RS)-α-(2-Benzylhydrazino)propionic Acid (IIa).

A solution of pyruvic acid (3.2 g, 36 mmoles), benzoylhydrazine (5 g, 36 mmoles) and sodium bicarbonate (3.5 g) in water (50 ml) was stirred at room temperature for 16 hours. The solution was acidified with dilute hydrochloric acid and the precipitate (α-benzoylhydrazonopropionic acid) was collected and dissolved in water (25 ml) with sodium bicarbonate (2.5 g). The resulting solution was treated portionwise under vigorous stirring with 2% sodium amalgam (50 g, 43.5 mg-atoms) at 0-5°. After 1 hour at 15°, the aqueous suspension was separated from the mercury and filtered through a Celite pad, chilled and slowly acidified with concentrated hydrochloric acid. Concentration under vacuum to a small volume afforded 2.8 g (37%) of IIa, mp 131-133°; ir (oil mull): 3400, 3250 (NH, OH), 1720 (C=O), 1675 (C=O) cm^{-1}; nmr (hexadeuteriodimethylsulfoxide): 1.28 (d, CH_3, 3H, $J_{2,3}$ = 6.5 Hz), 3.67 (q, H—2, 1H), 7.30-7.95 (m, aromatic, 5H), 8.0 *ca.* (broad, NH and COOH, 3H).

Table 3

α-Acylhydrazinoacids Derivatives VI

Compound No.	R^1	R^2	R^3	X	Configuration	Yield %	Mp °C	$[\alpha]_D^{20}$, °, c = 1, chloroform	Molecular Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIa	CH_3	C_6H_5	CH_3	OCH_3	R	52	130-131	−8.9	$C_{12}H_{16}N_2O_3$	61.00	6.83	11.86	61.21	6.78	11.97
VIb	CH_3	C_6H_5	H	NHC_6H_{11}	R	78	165-167	−14.2	$C_{16}H_{23}N_3O_2$	66.41	8.01	14.52	66.49	8.11	14.75
VIc	H	CH_3	C_6H_5	$NHNH_2$	RS	77	119-121	—	$C_{10}H_{14}N_4O_2$	54.04	6.35	25.21	54.17	6.42	25.03
VId	CH_3	C_6H_5	CH_3		R	73	108-111	+23.4	$C_{25}H_{32}N_4O_7S$	56.37	6.06	10.52	56.25	6.13	10.65

General Procedure for the Preparation of Compounds IIb-e.

A solution of Ib (10 g, 55.5 mmoles) and acetic-formic anhydride (44 g, 0.5 mole) in pyridine (100 ml) was stirred at room temperature for 3 hours. The solution was then poured into dilute sulfuric acid and extracted with chloroform. The solvent was removed under vacuum and the residue was triturated with cyclohexane to yield 33 g (28%) of IIb, mp 129-131°; $[\alpha]_D = -104.8°$ (c = 1, 0.1*N* sodium hydroxide); ir (oil mull): 3220 (NH), 2620 and 2510 (OH), 1720 (C=O), 1660 cm^{-1} (C=O); nmr (tetradeuteriomethanol): two conformers, δ 2.65 and 2.70 (2 singlets, NCH_3, 3H), 4.51 and 4.75 (2 singlets, H-α, 1H), 7.32-7.70 (m, aromatic, 5H), 7.79 and 8.15 (2 singlets, CHO, 1H).

Dihydrooxadiazinones IIIa-f (Table 2).

Method A.

Ex. *(R)*-4-Methyl-5-phenyl-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one (IIIb).

A solution of IIb (1 g, 4.8 mmoles) and DCC (2 g, 10 mmoles) in tetrahydrofuran (30 ml) was stirred at room temperature for 1 day. The precipitate was filtered and the solvent was removed under vacuum. Trituration of the residue with cyclohexane afforded a solid which was collected and chromatographed over freshly activated silica gel (hexane-ethyl acetate 7:3) to yield 0.68 g (78%) of IIIb, mp 74-75°, $[\alpha]_D = -87.1°$ (c = 1, chloroform); ir (oil mull): 1800 (C=O), 1640 cm^{-1} (C=N); nmr (deuteriochloroform): 2.68 (s, CH_3, 3H), 4.35 (s, H—5, 1H), 6.92 (s, H—2, 1H), 7.46 (m, aromatic, 5H).

Method B.

Ex. *(RS)*-4,5-Diphenyl-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one (IIId).

A solution of IId (540 mg, 2 mmoles) in acetic anhydride (20 ml) was stirred at 40° for 3 hours. The solvent was removed under vacuum and the residue was crystallized from 2-propanol to yield 400 mg (79%) of IIId, mp 146-148°; ir (oil mull): 1795 (C=O), 1600 cm^{-1} (C=N); nmr (deuteriochloroform): δ 6.05 (s, H—5, 1H), 6.95 (s, H-2, 1H), 7.05-7.40 (m, aromatic, 10H).

(R)-2,4-Dimethyl-5-phenyl-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one (IIIc).

A suspension of Ib (1 g, 5.55 mmoles) in acetic anhydride (30 ml) was stirred at room temperature for four days. The solvent was removed under vacuum and the residue crystallized from 2-propanol to yield 1 g (88%) of IIIc, mp 70-71°, $[\alpha]_D = -105.8°$ (c = 1, chloroform); ir (oil mull): 1790 (C=O), 1675 cm^{-1} (C=N); nmr (hexadeuteriodimethylsulfoxide): δ 2.06 (s, C—CH_3, 3H), 2.48 (s, N—CH_3, 3H), 4.58 (s, H—5, 1H), 7.42 (m, aromatic, 5H).

(Z)-α-(Benzoylhydrazono)phenylacetic Acid (IV).

A solution of benzoylhydrazine (6 g, 41 mmoles) in ethanol (20 ml) was added to a stirred solution of phenylglyoxylic acid (6 g, 40 mmoles) in water saturated with sodium bicarbonate (60 ml). Stirring was continued at room temperature for 16 hours, then the solution was acidified with dilute hydrochloric acid and extracted with chloroform. The organic phase was evaporated under vacuum and the residue was crystallized from ethanol to yield 6.8 g (63%) of IV, mp 175° dec (lit [8] mp 162° dec, lit [9] mp 167° dec); ir (oil mull): 3280 (NH), 1700 (C=O), 1650 cm^{-1} (C=O), nmr (hexadeuteriodimethylsulfoxide): 7.30-8.00 (m, aromatic, 10H), 12.50 (broad, NH and COOH, 2H).

2,5-Diphenyl-6*H*-1,3,4-oxadiazin-6-one (V).

A solution of IV (1 g, 3.7 mmoles) and DCC (1.5 g, 7.5 mmoles) in tetrahydrofuran (30 ml) was stirred at room temperature for 16 hours. The precipitate was filtered and the solvent removed under vacuum. The residue was triturated with cyclohexane and crystallized from 2-propanol to yield 0.6 g (65%) of V, mp 139-141° (lit [9] mp 139-140°).

(RS)-2,5-Diphenyl-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one (IIIe).

A solution of V (2 g, 8 mmoles) in acetic acid (50 ml) was treated portionwise with zinc dust (6.5 g, 0.1 g-atom) and stirred at room temperature for 30 minutes.The precipitate was filtered off and the solvent was removed under vacuum. The residue was crystallized from 2-propanol to

yield 1.1 g (55%) of IIIe, mp 159-161°; ir (oil mull): 3300 (NH), 1800 (C=O), 1650 cm^{-1} (C=N).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.10. Found: C, 71.12; H, 4.85; N, 11.21.

Reaction of Oxadiazinones with Nucleophiles (Table 3).

Methyl *(R)*-α-(2-Acetyl-1-methylhydrazino)phenylacetate (VIa).

A solution of IIIc (1 g, 4.9 mmoles) in methanol (50 ml) was left at room temperature for seven days. Evaporation of the solvent gave a residue, which was chromatographed over silica gel (ethyl ether) to afford 0.6 g (52%) of VIa, mp 130-131°; $[\alpha]_D = -8.9°$ (c = 1, chloroform); ir (oil mull): 3320 and 3200 (NH), 1750 (C=O), 1670 cm^{-1} (C=O); nmr (deuteriochloroform): two conformers, δ 1.73 and 1.77 (2 singlets, $COCH_3$, 3H), 2.67 and 2.76 (2 singlets, NCH_3, 3H), 3.70 and 3.73 (2 singlets, OCH_3, 3H), 4.56 and 5.00 (2 singlets, H—α, 1H), 7.38 (m, aromatic, 5H).

(R)-N-Cyclohexyl-α-(2-formyl-1-methylhydrazino)phenylacetamide (VIb).

A solution of IIIb (100 mg, 0.53 mmole) and cyclohexylamine (0.06 ml, 0.55 mmole) in tetrahydrofuran was stirred at room temperature for 3 hours. The precipitate was collected to afford 120 mg (78%) of VIb, mp 165-167°; $[\alpha]_D = -14.2°$ (c = 1, chloroform); ir (oil mull): 3480, 3320, 3200 and 3100 (NH), 1690 and 1650 cm^{-1} (C=O); nmr (hexadeuteriodimethylsulfoxide): two conformers, δ 0.95-2.05 (m, ring CH_2, 10H), 2.45 and 2.54 (2 singlets, CH_3, 3H), 3.60 (m, ring CH, 1H), 4.28 and 4.48 (2 singlets, H—α, 1H), 7.50 (m, aromatic, 5H), 7.92 (broad) and 8.15 (d, J = 10.5; CHO, 1H), 8.20 (broad, amide NH, 1H), 8.85 (d, J = 10.5 Hz) and 9.25 (broad, hydrazide NH, 1H).

(RS)-2-(2-Benzoylhydrazino)propionohydrazide (VIc).

A solution of IIIa (300 mg, 1.58 mmoles) and hydrazine hydrate (0.1 ml, 2.06 mmoles) in tetrahydrofuran (10 ml) was stirred at room temperature for 1 hour. The solvent was removed under vacuum and the residue was triturated with ethyl acetate to afford 270 mg (77%) of VIc, mp 119-121°; ir (oil mull): 3280 (NH), 1670 and 1650 cm^{-1} (C=O); nmr (hexadeuteriodimethylsulfoxide): δ 1.21 (d, CH_3, 3H, J = 5.6 Hz), 3.51 (q, CH, 1H), 4.17 (broad, NH_2, 2H), 5.22 (broad, NHN*H*CH, 1H), 7.30-7.90 (m, aromatic, 5H), 8.97 (broad, CON*H*NH_2, 1H), 9.68 (broad, C_6H_5—CON*H*, 1H).

t-Butyl 3-Acetoxymethyl-7β-[*(R)*-α-(2-acetyl-1-methylhydrazino)phenylacetamido]-3-cephem-4-carboxylate (VId).

A solution of IIIc (100 mg, 0.49 mmole) and *t*-butyl 3-acetoxymethyl-7-amino-3-cephem-4-carboxylate (160 mg, 0.49 mmole) in tetrahydrofuran (5 ml) was stirred at 50° for 5 hours. The solvent was evaporated under vacuum and the residue was triturated with 2-propyl ether to yield 190 mg (73%) of VId, mp 108-111°; $[\alpha]_D = +23.4°$ (c = 1, chloroform); ir (oil mull): 3300 (NH), 1780, 1730, 1720 and 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.55 (s, C—CH_3, 9H), 1.80 (s, CH_3CON, 3H), 2.09 (s, CH_3COO, 3H), 2.62 (s, NCH_3, 3H), 3.49 (broad s, CH_2, 2H), 4.60 (s, C_6H_5CH, 1H), 4.84 and 5.16 (ABq, $COOCH_2$, 2H, J = 13 Hz), 5.01 (d, H—6, 1H, J = 5.6 Hz), 5.83 (dd, H—7, 1H, J = 10.6 and 5.6 Hz), 6.62 (s, CH_3CONH, 1H), 7.41 (m, aromatic, 5H), 8.95 (d, CONHceph, 1H, J = 10.6 Hz).

Acknowledgement.

The authors gratefully acknowledge Dr. R. Erba for spectroscopic assistance and Dr. M. T. Riccaboni for the collaboration in the redaction of the manuscript.

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