Δ^3- and Δ^4-1,2,4-Oxadiazolin-5- and 3-ones

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Preparations for 2,3-diphenyl- and 2-benzyl-3-phenyl-Δ^3-1,2,4-oxadiazolin-5-ones (**3**) and (**4**) and for 2,5-diphenyl-Δ^4-1,2,4-oxadiazolin-3-one (**7**) are reported.

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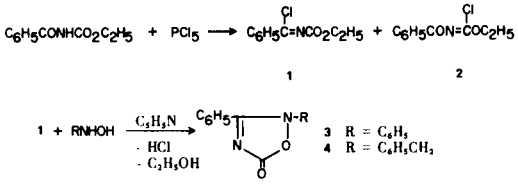
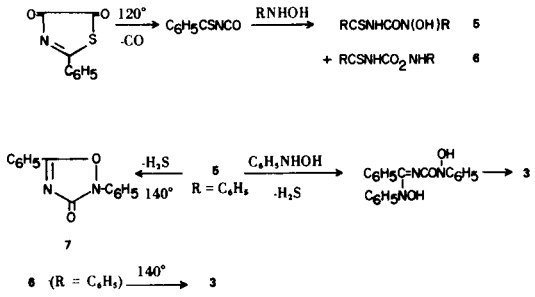
Of the three known simple oxadiazolinone ring systems (a total of six when mesoionic and fused ring systems are excluded) the most common are the Δ^2-1,2,4-oxadiazolin-5-ones whereas there are nine known examples of Δ^3-1,2,4-oxadiazolin-5-ones and five of the Δ^4-1,2,4-oxadiazolin-3-ones.

The 2,3-diphenyl- and 2-benzyl-3-phenyl-Δ^3-1,2,4-oxadiazolin-5-ones (**3**) and (**4**) were required for comparison with the corresponding Δ^2-1,2,4-oxadiazolin-5-ones (2) in thermolytic and photolytic ejection of carbon dioxide (1).

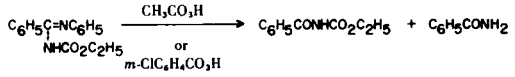
Benzoylurethan was transformed into a mixture of ethyl α-chlorobenzylidene carbamate (**1**) and ethyl *N*-benzoylchloroformimidate (**2**) by treatment with phosphorus pentachloride (3). The carbamate **1** was then treated with the appropriate hydroxylamine to give the oxadiazolinone **3** (15%) and **4** 60%). Neither of the intermediate *N*-hydroxyamidines was isolated.



In another procedure, thiobenzoyl isocyanate was liberated from 2-phenylthiazoline-4,5-dione by heating in *o*-xylene at 120° (4) and treated with a molar excess of phenylhydroxylamine in anhydrous ether. The evolution of hydrogen sulfide was completed by heating at reflux. From the reaction mixture 2,5-diphenyl-Δ^4-1,2,4-oxadiazolin-3-one (**7**) (79%), the oxadiazolinone **3** (7%), thiobenzamide (9%), benzamide (3%) and unidentified oils were obtained. The similar reaction with benzylhydroxylamine produced the oxadiazolinone **4** (18%).



Attempts to oxidize *N*-phenyl-*N'*-carboethoxybenzamidine (5) into its nitrone gave instead ethyl *N*-benzoylcarbamate and benzamide. This precluded an investigation on the anticipated ring-closure of the nitrone into the oxadiazolinone **1**.



EXPERIMENTAL

Instruments included Cary 14 uv and Perkin-Elmer 237B grating ir spectrophotometers, Varian A-60 nmr spectrometer, AEI Scientific Apparatus Limited MS 30 double beam mass spectrometer and a Bausch and Lomb refractometer. Elemental analyses were carried out by Micro Tech Laboratories, Inc., Skokie, Illinois. Melting points and boiling points were uncorrected. The following compounds were commercially available: azoxybenzene (m.p. 86-87°), benzamide (125-126°), *N*-benzoylurea (m.p. 215-217°), and thiobenzamide (108-109°). The following compounds were described in the literature: benzoyl isocyanate (6) (b.p. 30°/0.005 mm), ethyl *N*-benzoylcarbamate (6) (m.p. 110-111°), *N*-phenylhydroxylamine (7) (m.p. 80-81°), *N*-benzylhydroxylamine (8) (m.p. 51-53°), 2-phenylthiazoline-4,5-dione (9) (m.p. 168-171° dec.), and *N*-phenyl-*N'*-benzoylurea (6) (m.p. 209-210°).

Ethyl-α-chlorobenzylidenecarbamate (3).

To a suspension of 9.65 g. (0.05 mole) of ethyl *N*-benzoylcarbamate in 50 ml. of anhydrous toluene cooled to 0°, 10.40 g. (0.05 mole) of phosphorus pentachloride was added. The suspension was stirred at 0° until the solids had dissolved (3 hours). Toluene was removed and a viscous yellow oil residue was distilled. The forerun was identified as benzoyl isocyanate (**4**→C_6H_5CONCO + C_2H_5Cl) by comparison of its ir with authentic data (10). The next fraction gave 5.59 g. (0.026 mole, 53%) of colorless ethyl α-chlorobenzylidenecarbamate, b.p. 109-111°/0.05 mm (lit. (3) b.p. 100-103°/0.05 mm); n_D^{20} = 1.5420; ir (neat): 1773 and 1715 (sh) (C=O) and 1658 cm^{-1} (C=N); nmr (deuteriochloroform): δ 8.23-8.00 (m, 2, ArH), 7.77-7.33 (m, 3, ArH), 4.42 (m, 2, CH_2, J = 7.5 Hz), 1.40 (t, 3, CH_3, J = 7.5 Hz). A residue of 0.25 g. (1.3 mmoles) of ethyl *N*-benzoylcarbamate remained. Ethyl *N*-benzoylcarbamate partially sublimed during distillation; however, two Kugelrohr distillations (0.15 mm) with an oven temperature of 125° gave purified ethyl α-chlorobenzylidenecarbamate.

2,3-Diphenyl-Δ^3-1,2,4-oxadiazolin-5-one.

A. From Ethyl α-Chlorobenzylidenecarbamate.

In a 50 ml. three-neck round bottom flask fitted with an addition funnel, a mechanical stirrer, and gas inlet and outlet tubes 0.632 g. (3 mmoles) of ethyl α-chlorobenzylidenecarbamate in 10 ml. of anhydrous toluene was stirred at 0° under

nitrogen. After combining 0.635 g. (5.85 mmoles) of *N*-phenylhydroxylamine in 15 ml. of anhydrous toluene and 1 ml. of anhydrous pyridine the mixture was held at 0° for 15 hours and then heated at 50° for 2 hours. The reaction mixture was cooled, extracted twice with 10 ml. of 2 *N* hydrochloric acid and once with 10 ml. of water and then dried (magnesium sulfate). The filtered solution was concentrated to a dark brown oil (0.747 g,) which was chromatographed from 12 g. of silica gel. Elution with hexane-benzene (9:1) gave 333 mg. (1.68 mmoles) of azoxybenzene, confirmed by comparison of its ir, tlc and gc retention time with authentic data. Hexane-benzene (7:3) eluted 50 mg. (0.208 mmoles, 7%) of *N*-phenyl-*N'*-benzoylurea (11) as a colorless solid, m.p. and mixed m.p. 206-207°, whose ir, mass spectrum, and tlc were identical with authentic data. Elution with hexane-benzene (1:1) afforded 107 mg. (0.450 mmole), (15%) of colorless 2,3-diphenyl-Δ^3-1,2,4-oxadiazolin-5-one, sublimation at 100° (0.01 mm) confirmed by comparison of its ir, tlc plate and mass spectrum with authentic data from a sample prepared from *N*-phenylhydroxylamine and thiobenzoyl isocyanate.

b. From Thiobenzoyl Isocyanate and *N*-Phenylhydroxylamine.

After 1.0 g. (5.2 mmoles) of 2-phenylthiazoline-4,5-dione in 10 ml. of *o*-xylene was heated at 120° for 7 minutes, the violet solution was cooled in an ice-salt bath to -5°, treated with 1.09 g. (10.0 mmoles) of *N*-phenylhydroxylamine in 7 ml. of anhydrous ether, stirred for 30 minutes, and refluxed until the evolution of hydrogen sulfide had ceased. After dilution with 10 ml. of ether, the pale yellow solution at 0° gave 2,5-diphenyl-Δ^4-1,2,4-oxadiazolin-3-one as a colorless precipitate, 835 mg. (68%), m.p. 131-131.5° after recrystallization from carbon tetrachloride; ir (dichloromethane): 3080, 3010, 1714 (s), 1721 (s), 1622, 1615, 1598, 1576, 1497, 1464, 1451, 1366, 1399, 1322, 1293, 1201, 1178, 1120, 1065, 1023, 990, 976, 939, 930, 900 cm^{-1}; nmr (deuteriochloroform): δ 7.22-8.19 (m, Ar-H); uv λ max (cyclohexane): (ϵ) 235sh (12,200), 252 (14,800), 281 (5,900), 290 nm (5,900); ms: (70 ev) m/e (relative intensity) M^+ 238 (100), 119 (4), 105 (11), 103 (7), 91 (33), 77 (12), 76 (3), 64 (7), 58 (23).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.45; H, 4.05; N, 11.75.

After solvent was removed from the ether soluble fraction, the residue was taken up in 10 ml. of methylene chloride and extracted twice with 4 ml. of 2 *N* hydrochloric acid and with water. The organic layer was dried (magnesium sulfate), filtered, concentrated by evaporation, and treated with 2 ml. of ether to precipitate 168 mg. of colorless solid at 0°. The solid was dissolved in a benzene-carbon tetrachloride (3:2) mixture and chromatographically separated from 7 g. of silica gel. The same solvent mixture eluted 108 mg. (0.45 mmole, 9%) of the Δ^4-oxadiazolone followed by 61 mg. (0.26 mmole, 5%) of 2,3-diphenyl-Δ^3-1,2,4-oxadiazolin-5-one; m.p. 141-142.5°; ir (dichloromethane): 3062, 1179 (s), 1608, 1591, 1528, 1500, 1453, 1429, 1403, 1320, 1292, 1265, 1149, 1078, 1031, 1008, 953, 855 cm^{-1}; nmr (deuteriochloroform): δ 7.2-7.7 (m, Ar-H); uv λ max (methanol): (ϵ) 202 (31,900), 250 mm (16,400); ms: (70 ev) m/e (relative intensity) M 238 (13), 222 (8), 194 (33), 180 (12), 119 (2), 103 (20), 91 (100), 77 (23), 76 (10), 65 (45), 64 (15), 51 (14), 44 (15).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; C, 4.23; N, 11.76. Found: C, 70.31; H, 4.17; N, 11.71.

The ether soluble fraction (316 mg.) was taken up in a benzene-carbon tetrachloride (3:2) mixture and chromatographed from 14 g. of silica gel from which there was obtained 177 mg. of unidentified oils, 61 mg. (0.45 mmole, 9%) of thiobenzamide, m.p. and mixed m.p. 107.5-109°, and 25 mg. (0.11 mmole, 2%, total yield, 79%) of the Δ^4-oxadiazolone eluted with the same solvent mixture. Elution with a benzene-chloroform (1:1) mixture gave 23 mg. (0.10 mmole, 2%, total yield, 7%) of the Δ^3-oxadiazolone followed by 16 mg. (0.13 mmole, 3%) of benzamide, m.p. and mixed m.p. 124-124.5°.

The aqueous layer was neutralized with sodium bicarbonate, saturated with sodium chloride and thoroughly extracted with methylene chloride. After the solvent was dried (magnesium sulfate) and filtered, it was evaporated under reduced pressure to give 376 mg. (3.45 mmoles) of *N*-phenylhydroxylamine identified by its infrared spectrum and underpressed mixture melting point.

2-Benzyl-3-phenyl-Δ^3-1,2,4-oxadiazolin-5-one.

a. From Ethyl α-Chlorobenzylidenecarbamate and *N*-Benzylhydroxylamine.

In a 100 ml. two-neck round bottom flask fitted with a condenser and gas inlet and outlet tubes 5.700 g. (0.043 mole) of *N*-benzylhydroxylamine in 30 ml. of 1,2-dichloroethane and 3 ml. (0.036 mole) of anhydrous pyridine was stirred under nitrogen and treated with 4.381 g. (0.021 mole) of ethyl α-chlorobenzylidenecarbamate in 25 ml. of 1,2-dichloroethane added dropwise. The solution was stirred for one hour, refluxed for 3 hours, cooled and extracted twice with 45 ml. of 2 *N* hydrochloric acid. The combined acid extracts were washed with 20 ml. of methylene chloride. The combined organic extract was dried (magnesium sulfate) and filtered, and gave a dark brown oil after the solvent was removed under reduced pressure. The oil was dissolved in a hexane-benzene (1:1) mixture and passed over 200 g. of silica gel. Elution with a benzene-chloroform (3:1) mixture gave 3.124 g. (0.0124 mole, 60%) of 2-benzyl-3-phenyl-Δ^3-1,2,4-oxadiazolin-5-one as a viscous yellow oil, b.p. 155°/0.005 mm (dec.); ir (dichloromethane): 3012, 1776 (s), 1608, 1585, 1524, 1481, 1456, 1412, 1353, 1316, 1176, 1135, 1075, 1029, 1002, 966, 922, 855, cm^{-1}; nmr (deuteriochloroform): δ 7.70-7.25 (m, 5, Ar-H), 5.13 (s, 1, CH_2); uv λ max (methanol): (ϵ) 200 (27,200), 243 nm (12,400); ms: (70 ev) m/e (relative intensity) M 252 (1), 236 (<1), 208 (1), 194 (3), 105 (13), 104 (14), 103 (21), 92 (13), 91 (100), 77 (12), 76 (8), 65 (10), 51 (10).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.52; H, 5.06; N, 10.63.

Distillation (155°/0.005 mm) of the Δ^3-oxadiazolone resulted in extensive decomposition with partial transformation into 2,4,6-triphenyl-1,3,5-triazine established by comparison of its tlc plate with authentic data. The oxadiazolone also decomposed upon storage in the dark at room temperature after a period of one week. After purification of the Δ^3-oxadiazolone by column chromatography it was stored at 0° for several weeks without decomposition.

b. From Thiobenzoyl Isocyanate and *N*-Benzylhydroxylamine.

In a 100 ml. three-neck round bottom flask 300 mg. (1.56 mmoles) of 2-phenylthiazoline-4,5-dione and 8 ml. of *o*-xylene were heated under nitrogen at 120° for 7 minutes in a preheated oil bath. The violet solution was cooled to -5° and 380 mg. (3.09 mmoles) of *N*-benzylhydroxylamine in 4 ml. of anhydrous ether was added. The mixture was stirred for 5 minutes, heated at reflux until the evolution of hydrogen sulfide had ceased, treated with 5 ml. of ether, and cooled to precipitate 73 mg. (0.45 mmole, 29%) of *N*-benzoyl, m.p. and mixed m.p. 213-213.5°, confirmed by comparison of its ir and tlc plate with authentic data.

After the ether soluble fraction was extracted twice with 5 ml.

of 2 *N* hydrochloric acid, the organic extract was dried (magnesium sulfate), filtered, and concentrated. The residue was streaked onto a plate (20 x 20 cm) coated with 1 mm of silica gel. After the plate was developed in chloroform, a band at R_f = 0.19 gave 185 mg. of a crude mixture. Chromatographic separation from silica gel afforded 70 mg. (0.28 mmole, 18%) of 2-benzyl-3-phenyl-Δ^3-1,2,4-oxadiazolin-5-one verified by comparison of its ir and tlc plate with authentic data from a sample prepared from ethyl α-chlorobenzylidenecarbamate and *N*-benzylhydroxylamine.

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(10) Benzoyl isocyanate, detected by ir absorpition at 2250 cm^{-1} (NCO), was assumed to be a thermolysis product from the chloroformimidate **4**.

(11) Reduction of the condensate of the chloroformimidate and phenylhydroxylamine by excess hydroxylamine can account for the formation of *N*-phenyl-*N'*-benzoylurea.