4-Hydroxy-2-butenolide. A Versatile Reagent for the Synthesis of Heterocyclic Compounds

Francisco Yuste* and Rubén Sánchez-Obregón

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Mexico, DF, Mexico

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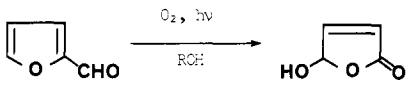
The base-catalyzed reaction of hydroxy lactone 1 with several cyclic and acyclic vinylogous amides and 1,3-dicarbonyl compounds was found to provide a smooth method to prepare pyrrole, furan, tetrahydroindole, and tetrahydrobenzofuran ring systems. The reaction of 1 with the cyclic enaminone 2 affords 3 which can be isomerized to the tetrahydroindole-2-acetic acid 4. The reaction of 1 with 6 and 8 produces, after esterification, the methyl tetrahydroindole- and pyrrole-2-acetates 7a and 9a, respectively. With acyclic 1,3-dicarbonyl compounds, 1 reacts to give furan-2-acetic acids, whereas the reaction of 1 with cyclic β-diketones leads to furo[3,2-*b*]benzofuran derivatives. The latter can be easily isomerized by heating with diluted acid to the corresponding tetrahydrobenzofuran-2-acetic acids. A possible mechanism for these reactions is proposed.

As part of a study directed toward the synthesis of indole alkaloids, we recently prepared and studied the reactions of 4-hydroxy-2-butenolide (1, malealdehydic acid or *cis*-β-formylacrylic acid).[1] This compound has been used recently for the synthesis of 4-substituted butenolides by reaction with 2 equiv of organolithium derivatives.[2]

The present paper describes a series of base-catalyzed reactions of this lactone with vinylogous amides and 1,3-dicarbonyl compounds which provide simple and efficient synthetic routes to several heterocyclic 2-carboxymethyl-substituted compounds.

The hydroxy lactone 1 was prepared by the photooxidation of furfural using the procedure of Willette.[3]

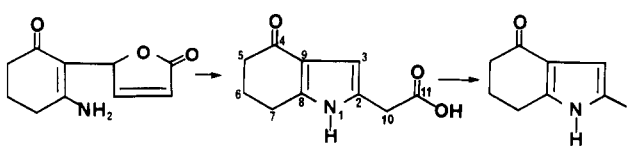


1

The base-catalyzed reaction of 1 with the enaminone 2 in ethanol at room temperature afforded a very insoluble crystalline solid in 83% yield. The IR, ^{1}H NMR, and mass spectral data suggested structure 3 for this compound, and the ^{13}C NMR spectrum (Table I) confirmed it.

2 1 3

Treatment of the enaminone 3 with base (5% Na_2CO_3, room temperature, 0.5 h) produced the 4-oxo-4,5,6,7-tetrahydroindole-2-acetic acid (4) in 54% yield. The ^{13}C NMR spectrum (Table I) allowed the assignment of this structure. Heating the acid 4 at 190–200 °C gave, in quantitative yield, the known 2-methyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (5).[4]

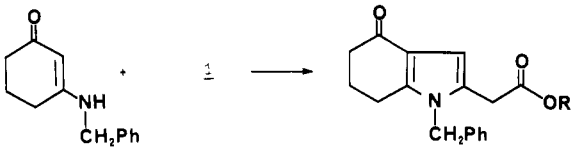


3 4 5

Table I. ^{13}C NMR Data for Compounds 3 and 4

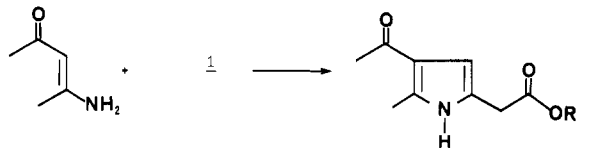
atom	shift, δ (multiplicity) 3	4
C-1	192.2 (s)	
C-2	100.3 (s)	119.6 (s)
C-3	166.5 (s)	103.4 (d)
C-4	29.6 (t)	192.3 (s)
C-5	20.6 (t)	37.6 (t)
C-6	36.6 (t)	22.1 (t)
C-7		23.7 (t)
C-8		125.8 (s)
C-9		143.3 (s)
C-10		33.0 (t)
C-11		171.4 (s)
C-2′	173.4 (s)	
C-3′	117.7 (d)	
C-4′	159.4 (d)	
C-5′	78.1 (d)	

Base-catalyzed reaction of the vinylogous secondary amide 6 with 1 at room temperature gave directly the tetrahydroindole-2-acetic acid 7, which was not isolated but was converted, by treatment with diazomethane, into the corresponding methyl ester 7a.



6 7, R = H
7a, R = Me

Similarly, the reaction of the acyclic vinylogous primary amide 8 with 1 under analogous conditions provided pyrrole 9, which was transformed, again without isolation, to the methyl ester 9a.



8 9, R = H
9a, R = Me

The reaction of lactone 1 with acyclic 1,3-dicarbonyl compounds 10 in refluxing ethanol in the presence of a

(1) Fecht, H. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1272.
(2) Machado-Araujo, F. W.; Gore, J. *Tetrahedron Lett.* **1981**, *22*, 1969.
(3) Doerr, I. L.; Willette, R. E. *J. Org. Chem.* **1973**, *38*, 3878.
(4) Tamura, Y.; Yoshimura, Y.; Nishimura, T.; Kato, S.; Kita, Y. *Tetrahedron Lett.* **1973**, 351.

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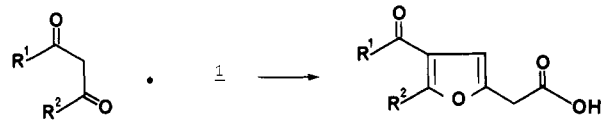
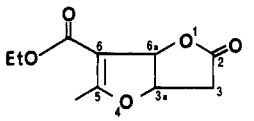
catalytic amount of either 2% aqueous sodium hydroxide or triethylamine follows a reaction course similar to that of the enaminones to afford the furans 11.



10a, R^1 = OEt; R^2 = Me
b, R^1 = R^2 = Me

11a, R^1 = OEt; R^2 = Me
b, R^1 = R^2 = Me

If the reaction of 1 with ethyl acetoacetate (10a) is carried out at room temperature, a crystalline product consisting of a mixture of isomers 12 and 11a (2:1 by NMR) is obtained.



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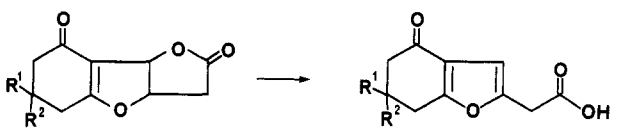
Heating with diluted acid converts the mixture to furan 11a in 70% yield.

The analogous reactions of the lactone 1 with cyclic β-diketones 13 led to tricyclic compounds 14 which could

13a, R = H
b, R = Me

14a, R = H
b, R = Me

be readily isomerized by heating with diluted acid to the substituted tetrahydrobenzofurans 15. Alternately, the



14a, R^1 = R^2 = H
b, R^1 = Me; R^2 = H

15a, R^1 = R^2 = H
b, R^1 = Me; R^2 = H
c, R^1 = R^2 = Me

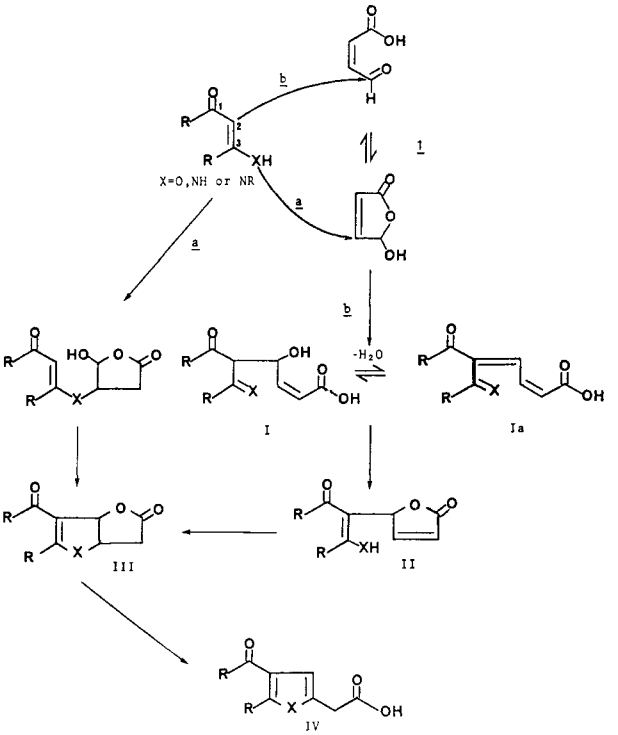
acids 15 can be obtained directly in one step without isolating the tricyclic intermediate. Accordingly, 15a and 15c were produced in 40% and 37% yields, respectively, from lactone 1.

Two reaction mechanisms (Scheme I) can be formulated for the reaction of lactone 1 with 1,3-dicarbonyl compounds or vinylogous amides; one involving initial O–C or N–C bond formation (pathway a) and the other involving initial C–C bond formation (pathway b).

Several references to the reactivity of 1,3-dicarbonyl compounds[5] or vinylogous amides[6] toward electrophiles support the proposed pathway b.

Here, the reaction is initiated by nucleophilic attack of the C-2 carbon of the dicarbonyl compounds or vinylogous amides on the aldehydic carbon of the acyclic tautomeric

Scheme I



form of compound 1. The resulting aldol I (or its dehydration product Ia) then forms the lactone II which can undergo an intramolecular Michael addition to afford compound III which finally isomerizes to the heterocyclic product IV. The fact that the Michael adducts III could be isolated in several cases coupled with the isolation of compound 3 supports the pathway b reaction mechanism.

Experimental Section

The melting points were taken on a Culatti capillary melting point apparatus and are corrected. Column chromatography was carried out by using Merck silica gel 60 (0.063–0.2 mm). The preparative TLC plates were of Merck silica gel 60 F-254 (20 × 20 × 0.2 cm). In order to follow the progress of the reactions or the purity of the compounds, we used Merck F-254 thin-layer plates (250 μm) cut into small slides (5 × 2.5 cm). The products were visualized by UV absorption or iodine vapor. Ultraviolet and infrared spectra were taken on Perkin-Elmer 552 and 283b instruments, respectively. NMR spectra were obtained on Varian HA-100 and FT-80A spectrometers in different solvents as indicated, with tetramethylsilane as an internal reference, and are expressed as δ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a Hewlett-Packard 5985-B spectrometer at 70 eV.

5-Hydroxy-2(5*H*)-furanone (1). This compound was prepared by using the procedure of Doerr and Willette.[3] Freshly distilled furfural (42.25 g, 0.44 mol) and 0.65 g of rose bengal in 425 mL of absolute ethanol were placed in a 500-mL Pyrex photochemical reaction vessel fitted with a fritted disk, thermometer, and reflux condenser. The solution was irradiated with a Norelco DYH (600 W, 120 V) lamp with bubbling from a vigorous stream of oxygen. The reaction temperature was kept between 25 and 32 °C, the lamp being cooled with a rapid stream of air. The end of the reaction was determined by the loss of UV absorption at 270 nm. After 8 h, a 95% decrease in absorption was observed. The solvent was evaporated to yield a reddish oil. The addition of 100 mL of carbon tetrachloride precipitated an orange solid (37.7 g) that was filtered and purified by chromatography on silica gel with chloroform as the eluent. By evaporation of the eluates and crystallization of the residue ($CHCl_3$) there was obtained 1: 19.9 g (42%); mp 58–60 °C (lit.[3] mp 56–58 °C); UV (MeOH) 207 nm; IR (film cast from $CHCl_3$) 3370, 1790,

(5) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 510.
(6) Bennett, G. B.; Simpson, W. R. J.; Mason, R. B.; Strohschein, R. J.; Mansukhani, R. *J. Org. Chem.* **1977**, *42*, 221 and references cited therein.

1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.25 (m, 3 H), 7.45 (d, J = 6 Hz, 1 H); ^{1}H NMR (sulfolane-d_8) δ 5.80 (br, 1 H, interchangeable with D_2O), 6.25 (d, J = 6 Hz, 2 H), 7.45 (d, J = 6 Hz, 1 H); MS, m/e (relative intensity) 100 (M^+, 14), 99 (23), 83 (7), 82 (6), 72 (46), 71 (25), 55 (100), 54 (49).

3-Amino-2-[2-oxofuran-5(*H*)-yl]-2-cyclohexen-1-one (3). To a solution of 1.11 g (10 mmol) of 3-amino-2-cyclohexen-1-one[7] and 1 g (10 mmol) of 1 in 50 mL of ethanol was added 1 mL of 2% sodium hydroxide. The resulting solution was stirred at 25 °C for 40 h. The crystals formed were filtered and washed with ethanol to give 1.60 g (83%) of **3** as very insoluble white crystals: mp 164–165 °C dec; IR (KBr) 3380, 3350, 3120 (br), 1730, 1685, 1590, 1545 cm^{-1}; IR (Nujol) 3375, 3350, 3120 (br), 1730, 1685, 1590, 1540 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ ~1.5–2.5 (m, 6 H), ~6.0 (m, 2 H), 6.95 (br, 2 H, interchangeable with D_2O), 7.70 (dd, J = 1, 5 Hz, 1 H); for ^{13}C NMR data, see Table I; MS, m/e (relative intensity) 193 (M^+, 70), 165 (75.5), 164 (86.5), 138 (100), 137 (94), 136 (37), 109 (36), 83 (42), 55 (41).

4,5,6,7-Tetrahydro-4-oxo-1*H*-indole-2-acetic Acid (4). A suspension of 193 mg (1 mmol) of **3** and 5 mL of 5% aqueous sodium carbonate was stirred at room temperature for 0.5 h. The resulting solution was acidified with 10% HCl and extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with a saturated brine solution, dried (Na_2SO_4), and evaporated, leaving a crystalline solid. Recrystallization from cold ethanol gave 105 mg (54%) of **4** as white crystals: mp 193 °C (CO_2↑); IR (KBr) 3440 (br), ~3100 (br), 1715, 1615, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ ~1.8–2.8 (m, 6 H), 3.50 (s, 2 H), 5.80 (br, 1 H, interchangeable with D_2O), 6.20 (s, 1 H, sharpened with D_2O), 10.55 (br, 1 H, interchangeable with D_2O); for ^{13}C NMR data see Table I; MS, m/e (relative intensity) 193 (M^+, 59), 165 (34), 148 (100), 137 (65).

1,5,6,7-Tetrahydro-2-methyl-4*H*-indol-4-one (5). The acid **4** (97 mg, 0.5 mmol) was heated in a Pyrex tube at 190–200 °C for 5 min. The resulting product was sublimated at 120–130 °C (0.1 mm) to give **5** as white crystals in quantitative yield: mp 199–200 °C (lit.[4] mp 204 °C); UV (MeOH) 208, 244, 285 nm; IR ($CHCl_3$) 3450, 1642 cm^{-1} (lit.[4] 3450, 1640 cm^{-1}); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ ~1.95–2.55 (m, 4 H), 2.20 (s, 3 H), 2.75 (t, J = 6 Hz, 2 H), 6.0–6.15 (m, 1 H), 9.60–10.35 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 149 (M^+, 77), 121 (56), 93 (100).

Methyl 4,5,6,7-Tetrahydro-1-(phenylmethyl)-4-oxo-1*H*-indole-2-acetate (7a). A solution of 201 mg (1 mmol) of *N*-benzyl-3-amino-2-cyclohexen-1-one,[8] 100 mg (1 mmol) of **1**, and 0.1 mL of 2% sodium hydroxide in 5 mL of ethanol was stirred at room temperature for 72 h. The crude product was treated with an excess of ethereal solution of diazomethane, and after the mixture was allowed to stand for 3 h, the volatiles were evaporated. The dark brown residue was chromatographed in two preparative chromatoplates by using ethyl acetate as the developing solvent. The elution and concentration of the eluate gave 178 mg (60%) of **7a** as a yellow oil homogeneous by TLC: IR (film) 1732, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ ~1.90–2.25 (m, 6 H), 3.45 (s, 2 H), 3.57 (s, 3 H), 5.10 (s, 2 H), 6.47 (s, 1 H), 6.70–6.95 (m, 2 H), 7.10–7.40 (m, 3 H); MS, m/e (relative intensity) 297 (M^+, 100), 239 (24), 238 (92), 91 (97).

Methyl 4-Acetyl-5-methyl-1*H*-pyrrole-2-acetate (9a). A solution containing 99 mg (1 mmol) of 4-amino-3-penten-2-one,[9] 100 mg (1 mmol) of **1**, and 1 drop of triethylamine in 5 mL of ethanol was stirred at room temperature for 12 h. The resulting acid was esterified with an excess of ethereal solution of diazomethane. The product was purified by preparative chromatography with ethyl acetate as the developing solvent. The evaporation of the eluates gave **9a** as a yellow oil: IR (film) 3250 (br), 1730, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 2.50 (s, 3 H), 3.55 (s, 2 H), 3.70 (s, 3 H), 6.25 (d, J = 2.5 Hz, 1 H), 8.50–9.25 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 195 (M^+, 30), 180 (13), 136 (100), 120 (23).

4-(Carboethoxy)-5-methylfuran-2-acetic Acid (11a). Method A. A solution of 650 mg (5 mmol) of ethyl acetoacetate, 500 mg (5 mmol) of the lactone **1**, and 0.3 mL of triethylamine in 10 mL of ethanol was stirred at room temperature for 16 h. Evaporation of the volatiles gave a residue that crystallized in the freezer: 800 mg (77%) of a mixture of **12** and **11a** (ca. 2:1 by ^{1}H NMR); IR (film cast from $CHCl_3$) 3700–2500 (br), 1780, 1705, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 and 1.30 (t, J = 7 Hz, 3 H), 2.26 and 2.50 (s, 3 H), ~2.90 (m, 2 H, CH_2 of **12**), 3.60 (s, 2 H, CH_2 of **11a**), 4.20 and 4.25 (q, J = 7 Hz, 2 H), 5.15 (m, 1 H, C-3a proton of **12**), 5.80 (d, J = 6 Hz, C-6a proton of **12**), ~5.95 (br, 1 H, interchangeable with D_2O), 6.45 (s, 1 H). The crystalline product was treated with 5 mL of 4:1 THF–0.1 N HCl and heated to reflux for 5 h. The volatiles were removed in vacuo, and the residue was treated with ether and extracted with 5% aqueous sodium bicarbonate. The aqueous phase was acidified and extracted with ether. Evaporation of the solvent gave an oily residue that crystallized on standing: 725 mg (70%) of yellow crystals; mp 71–73 °C. An analytical sample was obtained by sublimation at 50–55 °C (0.1 mm): white crystals; mp 75–76 °C; IR (film cast from $CHCl_3$) 3700–2500 (br), 1710 (br), 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 2.50 (s, 3 H), 3.60 (s, 2 H), 4.25 (q, J = 7 Hz, 2 H), 6.45 (s, 1 H), 8.90–9.45 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 212 (M^+, 36), 183 (24), 167 (100), 139 (53), 121 (72).

Method B. A solution of 260 mg (2 mmol) of ethyl acetoacetate, 200 mg (2 mmol) of the lactone **1**, and 0.2 mL of triethylamine was heated to reflux for 12 h. The product was purified as described in method A, giving 308 mg (73%) of **11a**. IR, ^{1}H NMR, and mass spectral data were identical with those given under method A.

4-Acetyl-5-methylfuran-2-acetic Acid (11b). A solution of 500 mg (5 mmol) of 2,4-pentanedione and 500 mg (5 mmol) of **1** in 10 mL of ethanol containing 0.5 mL of 2% sodium hydroxide was heated to reflux during 8 h. The solvent was evaporated, and the residue was treated with 5 mL of 5% sodium bicarbonate and extracted with ethyl acetate (2 × 20 mL). The aqueous phase was acidified and extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with brine (3 × 10 mL), dried, and evaporated. The oily residue after being crystallized from ethyl acetate–hexane afforded 600 mg (66%) of **11b**: mp 119 °C (lit.[10] mp 121.2–121.8 °C); IR (film cast from $CHCl_3$) 3500–2400 (br), 1705, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.55 (s, 3 H), 3.68 (s, 2 H), 6.48 (s, 1 H), 9.50 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 182 (M^+, 48), 167 (72), 137 (100), 43 (31).

3,3a,5,6,7,8b-Hexahydro-2*H*,8*H*-furo[3,2-*b*]benzofuran-2,8-dione (14a). A solution of 1.12 g (10 mmol) of 1,3-cyclohexanedione, 1 g (10 mmol) of lactone **1**, and 1 mL of 2% sodium hydroxide in 30 mL of ethanol was heated to reflux for 2 h. When the mixture cooled, the product crystallized. Recrystallization from cold ethanol gave 970 mg (50%) of **14a** as white crystals: mp 157–158 °C; UV (EtOH) 253 nm (ϵ 11 100); IR (KBr) 1770, 1660, 1650, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.90–2.75 (m, 6 H), 2.90–3.15 (m, 2 H), 5.45 (td, J = 7, 3 Hz, 1 H), 5.85 (d, J = 7 Hz, 1 H); MS, m/e (relative intensity) 194 (M^+, 36), 166 (100), 150 (51), 149 (37), 66 (36).

6-Methyl-3,3a,5,6,7,8b-hexahyro-2*H*,8*H*-furo[3,2-*b*]-benzofuran-2,8-dione (14b). A solution containing 252 mg (2 mmol) of 5-methyl-1,3-cyclohexanedione, 200 mg (2 mmol) of **1**, and 0.2 mL of triethylamine in 10 mL of ethanol was heated to reflux for 1 h. After the ethanol was evaporated, the residue was crystallized from chloroform–hexane to afford 160 mg of **14b** as white crystals. The mother liqueurs were chromatographed on two preparative chromatography plates with ethyl acetate as the developing solvent. The elution produced another 90 mg (60% yield) of product: mp 148–150 °C; IR ($CHCl_3$) 1780, 1660, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 5 Hz, 3 H), ~2.0–2.7 (m, 5 H), 2.86 (dd, J = 18, 2 Hz, 1 H), 3.14 (dd, J = 18, 7 Hz, 1 H), 5.42 (td, J = 7, 2 Hz, 1 H), 5.80 (d, J = 7 Hz, 1 H); MS, m/e (relative intensity) 208 (M^+, 21), 166 (100), 164 (45), 163 (28), 66 (27).

4,5,6,7-Tetrahydro-4-oxobenzofuran-2-acetic Acid (15a). Method A. A mixture of 97 mg (0.5 mmol) of tricyclic lactone **14a** and 12 mL of a solution of 4:1 THF–0.1 N HCl was heated

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(9) Lacey, M. J. *Aust. J. Chem.* **1970**, *23*, 841.
(10) Suverkropp, G. H.; Wynberg, H. *Chem. Ind. (London)* **1963**, 1803.

to reflux for 2.5 h. After cooling, the solution was poured into 10 mL of saturated sodium bicarbonate and extracted with ethyl acetate (3 × 30 mL). The aqueous phase was acidified and extracted with ethyl acetate (3 × 40 mL). The organic phase was washed with water (2 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave 66 mg (68%) of **15a**: mp 148–149 °C; UV (MeOH) 207, 264 nm; IR (KBr) ~3600–2500 (br), 1735, 1650, 1635 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.95–2.65 (m, 4 H), 2.85 (t, J = 5.5 Hz, 2 H), 3.65 (s, 2 H), 6.50 (s, 1 H), ~9.0 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 194 (M^+, 45), 166 (37), 149 (100), 138 (33).

Method B. A solution containing 112 mg (1 mmol) of 1,3-cyclohexanedione, 100 mg (1 mmol) of **1**, and 0.1 mL of 2% sodium hydroxide in 5 mL of ethanol was heated to reflux for 1 h. The ethanol was evaporated, the residue was treated with 5 mL of 4:1 THF–0.1 N HCl, and the resulting solution was heated to reflux for 2 h. After cooling, the solution was poured into 10 mL of saturated sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed, dried, and concentrated, affording 147 mg of **15a**. Recrystallization of acetone–hexane gave pure material: 78 mg (40%); mp 148–150 °C. The spectroscopic data were identical with those given under method A.

4,5,6,7-Tetrahydro-6-methyl-4-oxobenzofuran-2-acetic Acid (15b). To 104 mg (0.5 mmol) of lactone **14b** was added 10 mL of 4:1 THF–0.1 N HCl, and the resulting solution was heated to reflux for 3 h. The reaction mixture was allowed to stand overnight at room temperature, and then 20 mL of saturated sodium bicarbonate was added. The solution was extracted with ethyl acetate (2 × 20 mL). The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate (2 × 20 mL). The organic phase was washed, dried, and evaporated to give an oil that solidifies on standing: mp 146–147 °C; IR ($CHCl_3$) ~3400–2500 (br), 1715, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 7 Hz, 3 H), ~2.15–3.10 (m, 5 H), 3.70 (s, 2 H), 6.50 (s, 1 H), 8.45 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 208 (M^+, 100), 166 (97), 163 (94), 138 (44).

4,5,6,7-Tetrahydro-6,6-dimethyl-4-oxobenzofuran-2-acetic Acid (15c). A solution of 140 mg (1 mmol) of dimedone, 100 mg (1 mmol) of the hydroxy lactone **1**, and 0.1 mL of 2% sodium hydroxide in 5 mL of ethanol was heated for 1.5 h. The solvent was removed in vacuo, and the residue was treated with 5 mL of 4:1 THF–0.1 N HCl. The solution was heated to reflux for 2.5 h. After cooling, the solution was poured into 10 mL of saturated sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The aqueous phase was acidified with 1 N hydrochloric acid and extracted with ethyl acetate (3 × 10 mL). The extract was washed with water, dried, and concentrated. The residue was purified by preparative chromatography on two chromatography plates with ethyl acetate–methanol (90:10) as the developing solvent. The acetone eluates gave 83 mg (37%) of **15c** as yellow crystals: mp 110–112 °C; IR ($CHCl_3$) 3500, ~3300–2500 (br), 1715, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 6 H), 2.35 (s, 2 H), 2.70 (s, 2 H), 3.67 (s, 2 H), 6.50 (s, 1 H), 7.10–7.90 (br, 1 H, interchangeable with D_2O); MS, m/e (relative intensity) 222 (M^+, 30), 166 (100), 138 (30), 121 (23).

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Synthesis and Rearrangement of Pyrrolyl Sulfides and Sulfones[1]

Javier DeSales and Robert Greenhouse

Research Laboratories, Syntex, S.A., México 10, D.F., Mexico

Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, Palo Alto, California 94304

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A general synthesis of 3-pyrrolyl sulfides was developed on the basis of the triphenylphosphine–iodine–sodium iodide reduction of the sulfoxides, which in turn were obtained by the acid-mediated rearrangement of the corresponding 2-sulfinylpyrroles. Methods were also devised for the reduction of 2-(alkylsulfinyl)pyrroles to the sulfides. 2-Pyrrolyl and 3-pyrrolyl sulfides were shown to undergo acid-induced equilibration under mild conditions. With trifluoroacetic acid in dichloromethane solution, at room temperature, the equilibrium always was in favor of the 2-isomer and the interconversion appeared to be intramolecular. 2-(Methylsulfonyl)pyrrole and 2-(phenylsulfonyl)pyrrole were transformed into the 3-substituted isomers when heated under strongly acidic conditions.

We recently described single-step syntheses of 2-(arylsulfinyl)- and 2-(alkylsulfinyl)pyrroles and the acid-mediated transposition of these compounds into the 3-substituted isomers.[2] Inasmuch as the sulfoxide moiety is very easily reduced, it was obvious that the corresponding sulfides would be readily available, and, therefore, a study of their properties could be undertaken.

From the many methods that are available for the reduction of sulfoxides, three were chosen for study that are notable for their mildness. These were reduction by means of the systems triphenylphosphine–iodine–iodide (method A),[3] triphenylphosphine–carbon tetrachloride (method B),[4] and sodium borohydride–cobalt chloride (method C).[5] Of these method A was examined the most extensively. The reduction of the 3-pyrrolyl sulfoxides by this technique was

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