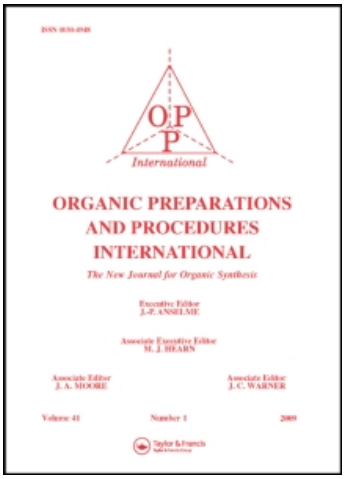

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2-ETHYL-2-(3-NITRO-4-HYDROXYPHENYL)-GLUTARIMIDE AND 2-ETHYL-2-(4-HYDROXYPHENYL)-GLUTARIMIDE

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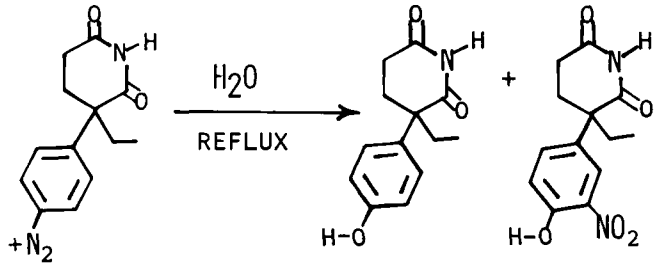
The search for and synthesis of biologically active metabolites of the drug glutethimide (Doriden®) recently begun,[1] required sizable quantities of 2-ethyl-2-(4-hydroxyphenyl)-glutarimide (II). One well-known method for the generation of phenols from aromatic amines involves the hydrolysis



I II III

of diazonium salts.[2] However, the hydrolysis of I by a known procedure[3] resulted in only a moderate yield (60%) of the desired phenol II and the formation of a mixture of compounds. In addition to II, a bright yellow compound was isolated and assigned structure III on the basis of its spectral data and elemental analysis results. 2-Ethyl-2-(3-nitro-4-hydroxyphenyl)-glutarimide (III), which had not previously been identified in this reaction mixture, has proven to be very valuable for the preparation of other important analogs and metabolites of glutethimide. Further, the isolation and identification of III provides an explanation for the moderate yields of II and gives added insight into possible side-reactions that may occur during the hydrolysis of similar diazonium salts.

EXPERIMENTAL

2-Ethyl-2-(4-hydroxyphenyl)-glutarimide (II) and 2-ethyl-2-(3-nitro-4-hydroxyphenyl)-glutarimide (III). To a stirred solution of 4 g (17.2 mmoles) of 2-ethyl-2-(4-aminophenyl)-glutarimide[3] in 150 ml of 2N H_2SO_4, cooled to 5° was slowly added 3.5 g (50.7 mmoles) of sodium nitrite dissolved in 10 ml distilled water, over a 15 min. period. The resulting clear solution of II was then added dropwise to 100 ml of boiling water which was maintained at reflux for 1 hour. After that time, the now dark red solution was cooled and extracted with excess methylene chloride. Evaporation of this extract yielded 4 g of a dark red oil containing approximately a 2:1 mixture of 2-ethyl-2-(4-hydroxyphenyl)-glutarimide (II) and 2-ethyl-2-(3-nitro-4-hydroxyphenyl)-glutarimide (III). The crude reaction mixture was chromatographed on a silica gel (28-200 mesh) column (3.5 x 20 cm). Elution with $CHCl_3$, containing 1% absolute ethanol resulted in the migration of a bright yellow band. This band was collected and after evaporation of the solvent yielded 1.5 g (31.3%) of III as yellow crystals, mp. 162-163° (uncorr.). Continued elution of two column volumes of 50% ethanol/$CHCl_3$ resulted in the elution of 2.4 g (60%) of II, as colorless crystals mp. 143-144° (uncorr.), lit.[3] mp. 143-144°, whose analytical data was identical to those previously reported.[3]

Thin layer (TLC) analysis using silica gel and a methylene chloride/acetone (95:5) solvent system, indicated I, R_f = 0.43 (bright yellow color), II, R_f = 0.15 and a trace third component R_f = 0.02 (orange color) which may result from other aromatic substitutions and oxidations. All these components readily reacted with diphenyl carbazone/mercuric sulfate (a dual TLC spray reagent specifically for the detection of imide ring systems).

2-Ethyl-2-(3-Nitro-4-Hydroxyphenyl)-glutarimide (III)- Mass spectrum:

M^+ = m/e 278 (30%), 251 (10%), 250 (70%), 249 (39%), 233 (14%), 232 (17%), 222 (9%), 221 (71%), 705 (7%), 204 (32%), 194 (12%), 193 (100%), 178 (21%), 164 (13%), 160 (14%), 132 (32%), 131 (15%), and 77 (20%).

Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.12; H, 5.04; N, 10.07

Found[4]: C, 56.01; H, 5.00; N, 9.86

NMR ($CDCl_3$/DMSO-d_6): 0.90δ (3H,t; CH_3-CH_2-, 1.95δ (2H,q;CH_3-CH_2-), 2.2.-2.6δ (4H,m; glutarimide ring protons), 5.0δ (1H; variable and broad, phenol), 7.1-7.9δ (3H,m. characteristic,[5] aromatic protons), and 8.9δ (1H,s, N-H); IR (KBr; cm^{-1}): 3270 (vs), 3100, 2985-2875 (sharp series), 1725 (vs), 1678 (vs), 1632, 1535 (vs), 1485, 1458, 1415, 1385, 1350-1250 (s; broad and diffuse), 1210-1130 (s, broad and diffuse), 850, 825, 765, and 615.

UV λ_{max}^{MeOH} : 370 nm and 355 nm; $\lambda_{max}^{MeOH/NH_4OH}$: 388 nm and 414 nm

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REFERENCES

1. B. D. Andresen, J. L. Templeton, R. H. Hammer, H. L. Panzik and M. J. Moldowan, Res. Comm. Chem. Pathol. and Pharm., 13, 193 (1976); Chem. Abstr. 84, 144, 9848.

2. A. I. Vogel,"Practical Organic Chemistry," 3rd Edition, Longmans Pub., London, (1972), p. 590-614.

3. H. Aboul-Enein, C. W. Schauberger, A. R. Hansen and L. J. Fischer, J. Med. Chem. 18, 736 (1975).

4. PCR, Inc., Gainesville, Florida.

5. C. J. Pouchert, and J. R. Campbell, "Aldrich Library of NMR Spectra," Vol. VIII, Aldrich Chemical Company, Milwaukee, Wisconsin, (1974), p. 168-C.

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