Preparation of 2-Methyl-3-(2-hydroxymethyl)phenyl-4(3*H*)-quinazalone: A Metabolite of Methaqualone

JAMES A. CELLA

Abstract □ The preparation of 2-methyl-3-(2-hydroxymethyl)-phenyl-4(3*H*)-quinazalone (I*b*), a metabolite of methaqualone [2-methyl-3-*o*-tolyl-4(3*H*)-quinazalone] (I*a*), is described. Bromination of I*a* is accomplished with *N*-bromosuccinimide in refluxing carbon tetrachloride. Solvolysis of this bromide (I*f*) in buffered diglyme–water affords I*b* in 86% yield.

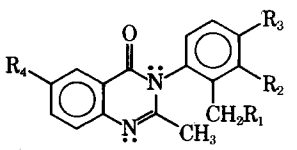
Keyphrases □ 2-Methyl-3-(2-hydroxymethyl)phenyl-4(3*H*)-quinazalone—methaqualone metabolite, synthesis □ Methaqualone—synthesis of metabolite 2-methyl-3-(2-hydroxymethyl)-phenyl-4(3*H*)-quinazalone

Methaqualone [2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone] (I*a*), a sedative hypnotic and often abused drug[1] (1), is detoxified by nonspecific hydroxylation; its principal metabolites are monohydroxy compounds I*b*–I*e* (2–4). The detection and quantification of these metabolites require standard samples for comparison. While the preparation of I*c*–I*e* is straightforward and has been described elsewhere (4, 5), no report has described the preparation of 2-methyl-3-(2-hydroxymethyl)phenyl-4(3*H*)-quinazalone (I*b*). Accordingly, a facile two-step preparation of I*b* is reported here.

Reaction of I*a* with a slight excess of *N*-bromosuccinimide in refluxing carbon tetrachloride afforded 2-methyl-3-(2-bromomethyl)phenyl-4(3*H*)-quinazalone (I*f*) in good yield. Solvolysis of I*f* in refluxing diglyme–water buffered with sodium carbonate afforded I*b* in 86% yield. The structure of I*b* was confirmed by spectroscopic and elemental analyses. Verification of I*b* as a metabolite of methaqualone has been accomplished by TLC (2, 3) and GLC (6, 7).

EXPERIMENTAL[2]

2-Methyl-3-(2-bromomethyl)phenyl-4(3*H*)-quinazalone (I*f*)—A solution of 250 mg (1 mmole) of methaqualone, 178 mg (1 mmole) of *N*-bromosuccinimide, and a trace of benzoyl peroxide in 25 ml of carbon tetrachloride was refluxed for 6 hr. Progress of the reaction was monitored by GLC. The reaction had to be reinitiated from time to time by addition of small amounts of benzoyl peroxide. Toward the end of the reaction, a slight excess of *N*-bromosuccinimide was added to convert more of the remaining methaqualone to product. The reaction was stopped when about 95% of the methaqualone had reacted. (Longer reaction times gave increased amounts of dibromination product at the expense of the desired product.)



I*a*: $R_1, R_2, R_3, R_4 = H$
I*b*: $R_2, R_3, R_4 = H; R_1 = OH$
I*c*: $R_1, R_3, R_4 = H; R_2 = OH$
I*d*: $R_1, R_2, R_4 = H; R_3 = OH$
I*e*: $R_1, R_2, R_3 = H; R_4 = OH$
I*f*: $R_2, R_3, R_4 = H; R_1 = Br$

The cooled mixture was shaken with 1.5 *N* sodium carbonate and brine and then dried by passage through a cone of anhydrous sodium sulfate. Evaporation of solvent afforded an oil (345 mg), the major (90–95%) component of which was shown by combined GLC–mass spectroscopy to be I*f*.

2-Methyl-3-(2-hydroxymethyl)phenyl-4(3*H*)-quinazalone (I*b*)—Crude I*f* was dissolved in 30 ml of a diglyme–1.5 *N* Na_2CO_3 mixture (5:1), and the resulting solution was refluxed for 6 hr. The cooled solution was diluted with an equal volume of water and extracted with 3 × 30 ml of chloroform. The dried (sodium sulfate) extracts were concentrated, and the residue was chromatographed on 10 g of silica gel to afford 230 mg (86%) of I*b*, mp 110–112° [lit. (8) mp 109–110°]; NMR ($CDCl_3$): δ 7.42 (m, 8, ArH), 4.22 (s, 2, CH_2OH), and 2.01 (s, 3, CH_3) ppm; IR (KBr): 6.02 ($\nu_{C=O}$) and 3.0 (ν_{OH}) μm; mass spectrum: *m/e* 267 (molecular ion) and 160 (loss of $ArCH_2OH$ from molecular ion).

Anal.—Calc. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.0; H, 5.3; N, 10.4.

[1] Trade names are Quaalude (Rorer), Sopor (Arnar-Stone), Optimil (Wallace), Parest (Parke-Davis), and Somnafac (Cooper).

[2] Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were recorded on a Beckman IR 5A spectrophotometer using sodium chloride disks or potassium chloride pellets. NMR spectra were recorded on a Varian A-60 spectrometer. Mass spectra were determined on a Hewlett-Packard 5930-A quadrupole mass spectrometer. GC was performed on an F&M model 402 high efficiency gas chromatograph, using a 1.8-m (6-ft) glass column packed with 3% OV-1 on 80–100-mesh Supelcoport. Microanalysis was performed by Mr. Joseph Alicino, New Hope, PA 18938. Methaqualone was obtained as a gift from Wm. H. Rorer & Co., Inc.

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