Hydrolytic Degradation of Methaqualone

JEROME J. ZALIPSKY ˣ, DAHYABHAI M. PATEL, and N. H. REAVEY-CANTWELL

Abstract □ The degradation products from acid and base hydrolysis of methaqualone, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, were isolated and identified by combined methods using liquid–liquid extraction, TLC, GLC, and IR, UV, and visible spectroscopy. Examination of the degradation products resulting from the hydrolysis of methaqualone revealed that, in boiling acidic or basic media, anthranilic acid, *o*-toluidine, and acetic acid were the major degradation components. The formation of the other degradation products, *N*-acetylanthranilic acid and 2-aminobenzo-*o*-toluidide, was acid–base strength dependent. The degradation of methaqualone in basic or acidic media followed different reaction pathways, but the primary decomposition was due to hydrolytic cleavage. The relationship between the degradation product, 2-aminobenzo-*o*-toluidide, and 2-nitrobenzo-*o*-toluidide, a metabolite of methaqualone in humans, is discussed.

Keyphrases □ Methaqualone—hydrolytic degradation, acid and base hydrolysis, isolation and identification of degradation products □ Hydrolysis—methaqualone, isolation and identification of degradation products, acid and basic media □ Degradation, methaqualone—acid and basic media, isolation and identification of products

In recent years there has been considerable interest in the pharmacology and chemistry of quinazolinone derivatives (1), and their hypnotic and sedative effects are of clinical interest (2–5). Methaqualone, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, is marketed both as a hypnotic and a sedative under various trade names. A monograph for it has been included in the British Pharmacopoeia (6). Although there have been several reports on the metabolic (7–9) and analytical (10–12) chemistry and bioavailability (13, 14) of methaqualone, little information is available concerning the degradative chemistry of this entity.

The purposes of this study were: *(a)* to investigate the degradative profile of methaqualone following acid and base hydrolysis, *(b)* to isolate and characterize the degradation products, and *(c)* to determine any differences in the formation products. This study was also conducted to find a possible correlation between *in vitro* degradation product(s) and *in vivo* metabolites (15).

EXPERIMENTAL

Apparatus—A dual-column gas chromatograph[1] was used with a 1.8-m × 0.3-cm (6-ft × 0.125-in.) o.d. stainless steel column (Column 1) packed with 10% UC W-98 Diatoport S, 80–100 mesh; with a 1.8-m × 0.3-cm (6-ft × 0.125-in.) o.d. stainless steel column (Column 2) packed with 5% neopentyl glycol succinate on Gas Chrom Z, 100–120 mesh; or with a 1.8-m × 0.3-cm (6-ft × 0.125-in.) o.d. stainless steel column (Column 3) packed with 10% Apiezon L on Diatoport S[2], 60–80 mesh. Flame-ionization detectors were used with nitrogen as a carrier gas (30 ml/min). The areas under the peaks were measured by electronic integrator.

IR spectral studies were carried out on a spectrophotometer[3] using KBr pellets. UV and visible spectra were determined on a recording spectrophotometer[4]. Conditions for TLC are described in Table I.

Procedure—A mixture of 1 g of methaqualone[5] and either 30 ml of 1.0 *N* NaOH, 30 ml of 0.1 *N* NaOH, or 30 ml of 1.2 *N* HCl was boiled separately in three round-bottom flasks for 7 hr. For each mixture, the volatile components were distilled through a horizontally positioned condenser into 20 ml of 0.1 *N* HCl (Solution A); the cooled reaction mixture was basified using 10% NaOH and extracted five times with 10-ml portions of ether, and the ether extracts were combined (Solution B); and the aqueous layer was acidified with 5 ml of 6 *N* HCl (Solution C).

Solutions A from the 1 *N* and 0.1 *N* NaOH reaction mixtures, after evaporation to dryness, each gave a crystalline solid. The solids were examined by UV (aqueous solution), TLC, and GLC using Column 2 (oven temperature 150°, injection temperature 180°, and detector temperature 200°). A reference sample of *o*-toluidine hydrochloride[6] was similarly analyzed.

Solutions B, after evaporation to dryness (under vacuum), gave solids which were analyzed by GLC using Column 1 (oven temperature 205°, injection temperature 230°, and detector temperature 250°) and by TLC. In addition, each solid was diazotized (16) and coupled with *N*-(1-naphthyl)ethylenediamine dihydrochloride[7], and the visible spectrum of the resulting purple solution was obtained. The reference samples of methaqualone and 2-aminobenzo-*o*-toluidide[5] were similarly analyzed.

Solutions C were extracted with 10 ml of chloroform, and each extract was analyzed by GLC using Column 3 (oven temperature 75°, injection temperature 150°, and detector temperature 200°). A reference sample solution of acetic acid in chloroform was similarly chromatographed. The aqueous layer of each Solution C was evaporated to dryness under a stream of air, and the resulting solid residue was dried at 60° for 3 hr. The residue was triturated with five 10-ml portions of ether; the ether extract, on treatment with 10 ml of a saturated hydrochloric acid–ether solution, gave a white precipitate which was subsequently filtered, washed, and dried at 60° for 2 hr. The ether filtrate was evaporated to dryness under a vacuum and the resulting solid was dried at 60° for 2 hr. The residue from the aqueous layer of each Solution C, the precipitate, and the solid recovered from the filtrate were examined by UV (methanol solution), TLC, and IR. The reference samples of anthranilic acid[6] and *N*-acetylanthranilic acid[6] were similarly analyzed.

RESULTS AND DISCUSSION

The isolation, identification, and confirmation of the degradation products of methaqualone following hydrolysis in basic and acidic media were accomplished by the use of the liquid–liquid extraction procedure followed by instrumental analyses. The degradation products of base and acid hydrolysis are presented in Scheme I.

Degradation Products from Boiling 1 *N* NaOH Solution—The condensed component trapped in 0.1 *N* HCl solution (Solution A) yielded 75 mg of solid I. The UV spectrum of I was compa-

[1] Hewlett-Packard model 7620A.
[2] Applied Science Laboratory, State College, Pa.
[3] Perkin-Elmer model 221.
[4] Cary model 14.
[5] William H. Rorer, Fort Washington, Pa.
[6] Eastman Kodak Co., Rochester, N.Y.
[7] Matheson, Coleman and Bell, East Rutherford, N.J.

Table I—TLC of Degradation Products

Degradation Product (Solvent System)[a]	Solution A (R_f)			Solution B (R_f)			Solution C (R_f)		
	1 *N* NaOH	0.1 *N* NaOH	1.2 *N* HCl	1 *N* NaOH	0.1 *N* NaOH	1.2 *N* HCl	1 *N* NaOH	0.1 *N* NaOH	1.2 *N* HCl
Anthranilic acid (A)	—	—	—	—	—	—	0.28	0.28	0.28
o-Toluidine (B)	0.15	0.15	—	—	—	—	—	—	0.15
2-Aminobenzo-*o*-toluidide (C)	—	—	—	0.88	0.88	—	—	—	—
N-Acetylanthranilic acid (D)	—	—	—	—	—	—	—	0.24	—
Unreacted methaqualone (C)	—	—	—	0.93	0.93	0.93	—	—	—

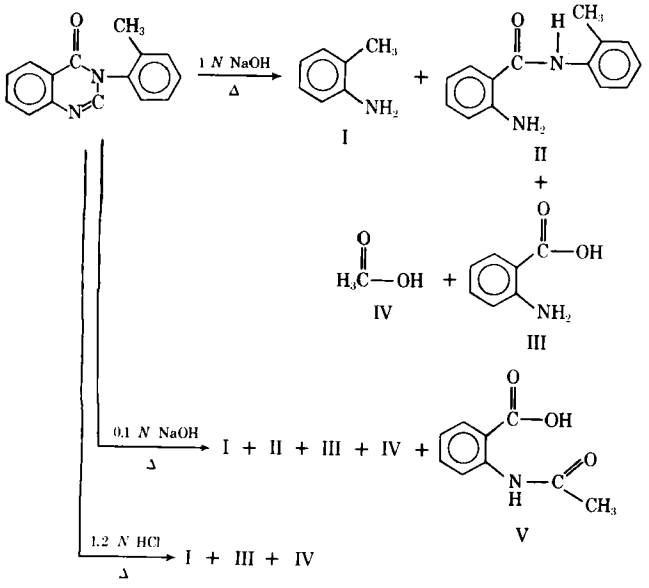
[a] A = ethanol–water (48:52), MN polyamide plate; B = chloroform–cyclohexane–acetic acid (50:40:10), silica gel plate; C = ether plus 2 drops of ammonium hydroxide, MN polyamide plate; and D = ethanol–water–acetic acid (48:52:10), MN polyamide plate. Chromatogram of silica gel G plate (Brinkmann Instruments, Inc., Westbury, N.Y.) was visualized in an iodine chamber. Chromatograms of Polyamide-11 (UV 254) plates (Brinkmann Instruments, Inc., Westbury, N.Y.) were visualized under short UV light.

rable with the reference spectrum of *o*-toluidine hydrochloride, showing three absorption maxima at 229, 266, and 279 nm. In addition, I was identified as *o*-toluidine by GLC (retention time of 3.25 min), TLC (Table I), and IR analysis (2860, 2620, 1600, 1500, 1145, and 752 cm^{-1}).

The ether extract (Solution B), after evaporation to dryness, yielded 772 mg of a solid containing a mixture of two components—80% of unreacted methaqualone and 20% of II; the latter was identified as 2-aminobenzo-*o*-toluidide by GLC with a retention time of 25.72 min (methaqualone = 22.82 min), TLC (Table I), and visible spectroscopy with a maximum absorption at 549 nm.

The aqueous acidified solution (Solution C) contained two components—anthranilic acid hydrochloride (III) and acetic acid (IV). Compound III was obtained after Solution C was extracted with chloroform and evaporated to dryness. The UV spectrum of III had two absorption maxima at 247 and 334 nm. Additional confirmation was obtained from TLC (Table I) and IR analysis (2975, 1690, 1460, 1390, 1215, 1101, 792, 758, and 751 cm^{-1}). Compound IV was extracted into chloroform and identified by GLC using Column 3 (retention time of 2.60 min).

Degradation Products from Boiling 0.1 *N* NaOH Solution—The separation and the identification of the degradation products resulting from the hydrolysis of methaqualone in 0.1 *N* NaOH solution were followed by the stated procedures. When analyzing Solutions A, B, and C, it was found that the yield of the degradation products decreased and a new product *N*-acetylanthranilic acid (V) had been formed. Solution A contained only a few milligrams of *o*-toluidine (I), and Solution B yielded only 6% of 2-aminobenzo-*o*-toluidide (II) and 94% of unreacted methaqualone as determined by GLC. Solution C contained a mixture of three components, which were identified as anthranilic acid hydrochloride (III), acetic acid (IV), and *N*-acetylanthranilic acid (V). Only a few milligrams of *N*-acetylanthranilic acid was found in the filtrate (ether extract) from which the anthranilic acid had been removed. The UV spectrum of V showed two absorption maxima at 252 and 302 nm. Additional confirmation was obtained from TLC (Table I) and IR analysis (3200, 2600, 1692, 1605, 1585, 1510, 1228, 790, and 768 cm^{-1}).



Scheme I

Degradation Products from Boiling 1.2 *N* HCl Solution—The hydrolysis of methaqualone in an acidic medium, in contrast to basic media, showed more extensive bond cleavage. The degradation products were identified as *o*-toluidine (I), anthranilic acid (III), and acetic acid (IV) by the stated methods. No other components, *e.g.*, *N*-acetylanthranilic acid or 2-aminobenzo-*o*-toluidide, which had been found in the basic media were present.

SUMMARY

A profile of the degradation products of methaqualone undergoing hydrolysis in boiling strong acid (1.2 *N* HCl) and strong bases (1.0 and 0.1 *N* NaOH) has been established. Under these stringent conditions, the low yields of the degradation products show that the molecule is relatively stable. None of the degradation products was comparable with the metabolites of methaqualone studied by Preuss *et al.* (17) and Nowak *et al.* (18). However, it was of interest to note that 2-aminobenzo-*o*-toluidide is the amino analog of a metabolite, 2-nitrobenzo-*o*-toluidide, isolated and identified by Murata and Yamamoto (15).

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[x] To whom inquiries should be directed.

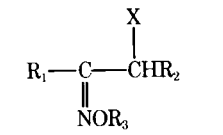
New Derivatives of 2-Alkoxyiminoalkylmercaptans as Potential Radioprotective Agents

SOU-YIE CHU, NORMAN L. HINES, and DOMINICK A. COVIELLO [x]

Abstract □ 2-Alkoxyiminoalkylmercaptans were treated with appropriate reagents by established procedures to prepare the corresponding "Bunte salts," 2-(2-alkoxyiminoalkylthio)-2-imidazolines, 2-(2-alkoxyimino)alkyl dithiocarbonates, and ethyl 2-alkoxyiminoalkyl trithiocarbonates. Selected compounds were screened for radioprotective activity, and none was found to have significant activity.

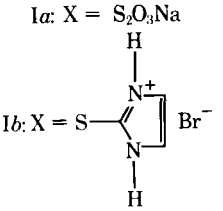
Keyphrases □ 2-Alkoxyiminoalkylmercaptan derivatives—synthesized as potential radioprotective agents □ Radioprotective activity—2-alkoxyiminoalkylmercaptan derivatives synthesized and screened □ Antiradiation agents, potential—synthesis and screening of 2-alkoxyiminoalkylmercaptan derivatives

The grouping of atoms N—C—C—S is apparently a good pharmacophore for antiradiation activity, since cysteamine (2-mercaptoethylamine) derivatives are among the most effective prophylactics against radiation damage. Since 2-alkoxyiminoalkyl bromides can be prepared by reacting *O*-alkyl ethers of aldoximes and ketoximes with *N*-bromosuccinimide (1), it was felt that they could be readily converted to 2-alkoxyiminomercaptan derivatives (I) incorporating the radioprotective pharmacophore. The bromides were reacted with sodium thiosulfate, ethylenethiourea, sodium *O*-ethyl dithiocarbonate, and sodium ethyl trithiocarbonate to yield "Bunte salts" (I*a*), 2-(2-alkoxyiminoalkylthio)-2-imidazolines (I*b*), ethyl *S*-(2-alkoxyimino) alkyl dithiocarbonates (I*c*), and ethyl 2-alkoxyiminoalkyl trithiocarbonates (I*d*), respectively, by established procedures (2–5). The yields and physical data of the compounds prepared are shown in Table I.



I

I*a*: X = S_2O_3Na



I*b*: X = S, Br^-

I*c*: X = $SCOSC_2H_5$

I*d*: X = $SCS_2C_2H_5$

Compounds III, XII, XVI, XX, XXI, XXV, and XXVIII were evaluated for radioprotective activity[1]. The test method was described (6) previously.

EXPERIMENTAL

Bunte Salts—The preparation of sodium *S*-(3-ethoxyimino-2-butyl)thiosulfate illustrates the general procedure.

A solution of 24.8 g (0.1 mole) of sodium thiosulfate pentahydrate in 50 ml of water was mixed with a solution of 19.4 g (0.1 mole) of 3-bromobutanone oxime *O*-ethyl ether in 30 ml of 95% ethanol. The mixture was stirred while heating with steam at reflux for 25 min. The resulting homogeneous solution was then evaporated to dryness under reduced pressure. The residue was extracted with 40 ml of ether, and the solution was cooled in the refrigerator overnight. The white amorphous crystals that formed were collected and dried in air to yield 4.4 g of the title compound. The mother liquor was taken to dryness on the flash evaporator, and the residue was taken up in 95% ethanol and treated with ether. The 7.2 g of product that precipitated melted at 162–164° dec.; total yield, 11.6 g (56.3%). Minor changes in the workup were all that distinguished the preparative methods for the various Bunte salts.

2-(2-Alkoxyiminoalkylthio)-2-imidazolinium Bromides—The general procedure was as follows. A mixture of ethylenethiourea (2.04 g, 0.02 mole) and bromoacetone oxime *O*-ethyl ether (3.96 g, 0.022 mole) in 15 ml of dimethylformamide was stirred at room temperature for 3 hr. Twenty-five milliliters of ether was added, and the resulting solution was cooled in an ice bath. A solid crystallized in white lustrous plates and was collected and washed with 10 ml of dimethylformamide–ether (1:1). The product weighed 5.0 g (air dried), mp 109–112°. From the mother liquor, 0.65 g of product was obtained by adding more ether and chilling the mixture. The total yield was 5.65 g (100%). The crude product

[1] At Walter Reed Army Institute of Research, Washington, D.C.