Table I—Salicylate Release from Microcapsules

Minutes	Salicylate Released[a], % Batch I[b]	Batch II[b]	Batch III[b]
1	4.5 (0.5)	4.0 (0.5)	3.9 (0.4)
5	10.0 (0.3)	10.1 (0.2)	10.2 (0.3)
10	18.1 (0.7)	17.0 (0.5)	17.5 (0.7)
15	27.5 (1.2)	28.3 (0.8)	28.0 (0.8)
25	38.0 (0.6)	37.7 (0.9)	38.1 (0.7)
35	47.5 (1.0)	48.0 (0.7)	48.2 (0.5)
50	58.3 (0.7)	58.9 (1.2)	58.5 (0.4)
65	70.0 (0.9)	71.0 (0.5)	71.0 (1.4)
80	83.5 (1.1)	84.1 (0.9)	83.7 (0.8)
100	93.1 (1.2)	92.5 (0.9)	93.5 (0.4)
120	100.0	100.0	100.0

[a] Each value is an average of at least two experiments. Values in parentheses indicate the ± range. [b] Each batch was prepared at a different time.

slowed the release significantly, increasing the time for complete drug release to about 2 hr.

Since sodium salicylate is readily water soluble, this amount of time corresponds to about a 103-fold increase in the time required for the complete dissolution of the drug particles.

The dissolution characteristics (Fig. 2) indicate that the release of sodium salicylate from the unhardened microcapsules approaches zero-order kinetics throughout much of the extraction process. For the hardened microcapsules, the dissolution shows essentially zero-order kinetics from about 30 to about 85% sodium salicylate release.

One aim with microencapsulation is to obtain zero-order drug release from the microcapsules (8). Unfortunately, experience shows that most microcapsule formulations release the drug at roughly a first-order rather than a zero-order rate (9). Figure 3 shows a first-order plot of sodium salicylate release from the microcapsules. While the unhardened microcapsules do not appear to follow first-order kinetics, the hardened microcapsules show a first-order release up to about 70% sodium salicylate released.

In most microencapsulation processes, microcapsule recovery involves a drying step that may influence the microcapsule integrity. For example, solvent evaporation during drying may cause shrinkage of the shell wall, thus creating coating defects, flaws, and/or deposition of a portion of the drug on the microcapsule surface due to the solvent migration effect. Because of these effects, either singly or in combination, the release patterns of the drug from the microcapsules may show an initial rapid drug release, which has been reported to range from about 10–20% (6) to as high as 50% (3). Since the microencapsulation process reported here uses gelation rather than drying, this effect was minimal in drug release from the microcapsules.

The microencapsulation process used in this investigation gave good reproducibility. Release rates obtained with the microcapsules from the same batch were within a narrow range, the maximum range observed being 3% (Table I). Duplicate batches of the microcapsules prepared at various times were identical to the original batch in terms of batch yield, microcapsule size and size distribution, and release rate profile. In addition, the process described is simple, economical, and amenable to industrial application.

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Synthesis of Methaqualone and Its Diphasic Titration in Pure and Tablet Forms

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Received April 4, 1977, from the *Departments of Pharmaceutical and Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, University of Alexandria, Alexandria, A.R. Egypt.* Accepted for publication June 13, 1977.

Abstract □ A one-step synthesis of methaqualone from *N*-acetylanthranilic acid and *o*-toluidine in the absence of a catalyst is described. A rapid diphasic titration procedure for its microestimation in pure and tablet forms, using dioctyl sodium sulfosuccinate and dimethyl yellow screened with oracet blue B, is proposed. The data were compared with those obtained from nonaqueous titration methods.

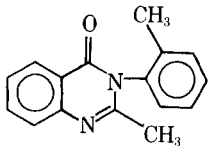
Keyphrases □ Methaqualone—one-step synthesis, diphasic titration analysis in bulk drug and tablets □ Titration, diphasic—analysis, methaqualone in bulk drug and tablets □ Hypnotic–sedatives—methaqualone, one-step synthesis, diphasic titration analysis in bulk drug and tablets

Methaqualone, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (I), is marketed both as a sedative–hypnotic and as an anticonvulsant (1). Several methods have been reported for its synthesis and evaluation as the base or hydrochloride in bulk drug and dosage forms.

Methaqualone has been synthesized by: (*a*) refluxing a solution of *N*-acetylanthranilic acid with *o*-toluidine in toluene in the presence of different catalysts (2–5); (*b*) by heating anthranilic acid, *o*-toluidine, acetic acid, and polyphosphoric acid (6); (*c*) by condensing 2-methyl-3,1,4-benzoxazone with *o*-toluidine (7, 8); or (*d*) by heating methyl anthranilate with *o*-toluidine *N*-(magnesium bromide) and acetylating the intermediate amide, which subsequently cyclizes (9). The hydrochloride of I was prepared by heating *N*-acetylanthranilic acid with *o*-toluidine hydrochloride (10).

For the estimation of I or its hydrochloride salt, diazometric (11), colorimetric (12), spectrophotometric (13, 14), complexometric (15), and nonaqueous titration (16–18) methods have been proposed.

In the present investigation, I was prepared by heating *N*-acetylanthranilic acid with *o*-toluidine in bromobenzene in the absence of a catalyst. This report also describes a



I

rapid diphasic titration analysis of I. The procedure is analogous to that applied for the microdetermination of secondary and tertiary organic bases and their salts (19).

The new method employed a previously standardized aqueous solution of dioctyl sodium sulfosuccinate (II) against a reference sample of I. The titration was conducted in a water–chloroform diphase at pH 1.09, using dimethyl yellow screened with oracet blue B dye as indicator. The method was used for methaqualone base and its tablet form, and the results were compared with those obtained from nonaqueous titration procedures (17, 18).

EXPERIMENTAL[1]

Synthesis of Methaqualone (I)—*N*-Acetylanthranilic acid (3.6 g, 0.02 mole) and freshly distilled *o*-toluidine (2.14 g, 0.02 mole) in bromobenzene (10 ml) were refluxed for 2.5 hr. Subsequently, nearly half of the volume of the solvent was distilled, and the dark reaction solution was mixed with benzene (30 ml). The solution was filtered, and the filtrate was extracted with 3 × 10 ml of hydrochloric acid (1:1). The acidic layer was purified by extraction with ether and then made alkaline (pH 8) with sodium hydroxide (25%). The crude semisolid product that solidified on standing was filtered, washed with water, and dried.

An analytically pure sample was obtained [yield of 2.3 g (48.4%)] by recrystallization from benzene–light petroleum (bp 40–60°) as colorless crystals, mp 112.5–113° [lit. mp 115–116° (2, 7), mp 120° (3), mp 113–115° (4, 5), and mp 113–114° (10)]; IR: 3100–2700 (CH_3) and 1670 (C=O) cm^{-1} and a band split at 1600, 1590, and 1560 cm^{-1} (C=N, C=C, and aromatics); ^{1}H-NMR: δ 2.02 (3H, s, CH_3 at C-2), 2.08 (3H, s, CH_3-*N*-tolyl), and 7.18–8.1 (8H, m, C-5, C-6, C-7, C-8, and *N*-tolyl) ppm; mass spectrum: *m/e* (relative intensity) 251 (10) (M + 1), 250 (50) (M^+), 249 (8) (M − 1), 236 (18), 235 (100), 234 (8), 233 (32), 239 (9), 206 (7), 167 (5), 166 (10), 165 (5), 152 (5), 143 (9), 132 (19), 125 (6), 124 (6), 117 (7), 116 (6), 109 (5), 104 (6), 103 (6), 102 (6), 92 (5), 91 (41), 90 (9), 89 (9), 85 (9), 83 (5), 77 (12), 76 (16), 75 (5), 69 (6), 68 (6), 67 (6), 65 (23), 63 (7), 51 (9), and 50 (11).

Anal.—Calc. for $C_{16}H_{14}N_2O$: N, 11.19. Found: N, 11.0.

Evaluation of Methaqualone (I) by Proposed Diphasic Titration Method—*Equipment*—Conventional laboratory glassware and a 10-ml microburet graduated to 0.02 ml were used.

Materials and Solutions—The following were used: methaqualone[2] dried in a vacuum desiccator to constant weight; methaqualone tablets[3]; a solution of dioctyl sodium sulfosuccinate[4] (II) (2.25 g) in distilled water (500 ml), prepared by gentle warming; chloroform[5]; pH 1.09 buffer, prepared by mixing 1 *N* sodium acetate[6] (200 ml) with 1 *N* HCl[6] (280 ml) and diluting to 1 liter with distilled water; and dimethyl yellow indicator[6] (15 mg) screened with oracet blue B dye (15 mg) in chloroform (500 ml).

Operational Parameters—The reference methaqualone base was the same microanalytically checked and spectroscopically studied sample. The aqueous solution of II was standardized by titration against the reference methaqualone following the procedure described later. For comparison purposes, the nonaqueous titration procedure of BP 1973 (17) for pure methaqualone and the literature (18) nonaqueous titration method for methaqualone tablets were performed.

Determination of Methaqualone Base—An accurately weighed amount of I (1–10 mg), contained in a 500-ml conical flask, was dissolved in 50 ml of chloroform. Distilled water (20 ml), pH 1.09 buffer (5 ml), and screened dimethyl yellow indicator (5 ml) were added, and the mixture was titrated against II with vigorous swirling. Toward the end-point, the titrant was added dropwise; the two phases were allowed to separate, and the mixture was swirled gently for 5 sec (the color of the end-point tended to concentrate between the two phases). The end-point was detected by a color change from green to pinkish gray in the bulk of the chloroform layer.

A blank determination was carried out. The percent recovery was calculated using:

$$\% \text{ recovery} = \frac{(V)(E)(100)}{\text{wt}} \qquad \text{(Eq. 1)}$$

where V is the milliliters of II used in the titration, E is the milligrams of I equivalent to 1 ml of the used II solution, and wt is the weight of I in milligrams.

Determination of Tablets—Twenty tablets were weighed and finely powdered. A quantity of the powder equivalent to about 8.0 mg of I was accurately weighed. Chloroform (50 ml), distilled water (20 ml), pH 1.09 buffer (5 ml), and screened dimethyl yellow indicator (5 ml) were added, and the mixture was titrated against II following the same procedure described for methaqualone in pure form. The content of the tablet was then calculated using:

$$\text{recovery of I per tablet} = \frac{(V)(E)(W_a)}{W_b} \qquad \text{(Eq. 2)}$$

where W_a is the average weight of the tablet and W_b is the weight of powdered tablets used in the assay.

RESULTS AND DISCUSSION

The synthetic route utilized in the preparation of I is believed to proceed *via* the initial formation of the intermediate *o*-acetamidobenz-*o*-tolylamide and subsequent loss of water. The structure of I was confirmed by elemental analysis, mass peak, and spectroscopic data. The predominant fragmentation process of I in the mass spectrum indicates the loss of a methyl radical from C-2, giving *m/e* 235 (III), which then fragments to *m/e* 91 ($CH_3C_6H_4$+) (IV) and 102 ($C_6H_4N^+{\equiv}C\cdot$) (V). The latter loses a cyanide radical to form the benzyne radical ion (*m/e* 76) (VI), which loses a hydrogen radical to give the benzyne cation (*m/e* 75) (VII).

The proposed diphasic titration procedure involves titration of I with II where a water-soluble complex is formed. When all I has reacted, any excess of II at pH 1.09 partitions into the chloroform phase as dioctyl hydrogen sulfosuccinate. The latter forms a chloroform-soluble colored complex with the screened dimethyl yellow indicator.

Comparative study of the results obtained using the proposed diphasic titration method with those using the compendial nonaqueous titration procedure of BP 1973 (17) for pure I was performed. The mean percent recoveries and standard deviations found were 99.9 ± 1.9 (average of 10 determinations) for the proposed diphasic method and 97.3 ± 2.4 (average of five determinations) for the BP 1973 procedure. This result revealed that the diphasic titration data were precise and could be satisfactorily used for the routine analysis of I. The described diphasic titration process was also advantageous because it excluded the limitation of working in nonaqueous media and was convenient for the microdetermination of I.

For the analysis of methaqualone tablets using the diphasic titration method, the mean recovery obtained (average of six determinations) was 148.9 ± 4.4 mg/tablet. For comparative study, the same tablets were determined using the potentiometric nonaqueous titration process described previously (18); and the mean recovery (average of five determinations) was 146.3 ± 2.5 mg/tablet. This nonaqueous titration method required preliminary separation of I from the tablets. In the present diphasic titration method, no previous isolation of I is necessary since ordinary tablet excipients and lubricants do not interfere. Moreover, the diphasic titration is timesaving when applied to the routine analysis of methaqualone tablets.

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[2] Prepared by the described new method.

[3] Especially made, for the present investigation, to contain 150 mg of I/tablet and calcium carbonate, starch, magnesium stearate, and talc as diluent and lubricant ingredients.

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S-(4-Chlorophenyl) 3-Aryl-3-hydroxypropanethioates as Antibacterial Agents

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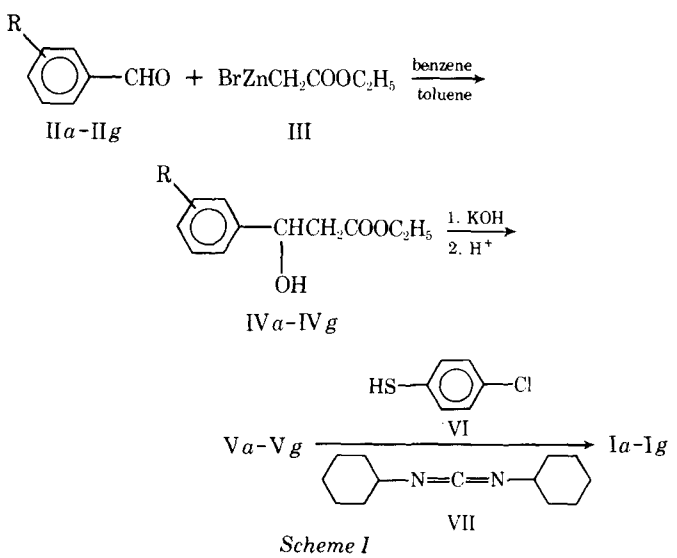
Abstract □ A series of *S*-(4-chlorophenyl) 3-aryl-3-hydroxypropanethioates was prepared and shown to have *in vitro* activity against several selected bacterial species.

Keyphrases □ 3-Hydroxypropanethioates, 3-aryl—series synthesized, antibacterial activity evaluated □ Antibacterial activity—3-aryl-3-hydroxypropanethioates evaluated □ Structure-activity relationships—3-aryl-3-hydroxypropanethioates evaluated for antibacterial activity

The usual pathway for fatty acid (both saturated and unsaturated) synthesis in bacteria is *via* thiol esters of coenzyme A intermediates (1–3). The enzyme responsible for the introduction of the double bond into the fatty acids of *Escherichia coli* is β-hydroxydecanoylthiol ester dehydrase (2, 3). This enzyme is vital for the growth of *E. coli* (2); its inhibition completely stops the growth of the bacterium (4, 5).

The required substrate for dehydrase preferably contains β-hydroxydecanoate as a thiol ester (2–4), which is dehydrated to a β,γ-unsaturated ester. It was postulated that a reasonable structure for a dehydrase inhibitor would possess a thiol ester of a β-hydroxy acid in which the γ-carbon is tertiary and, therefore, incapable of forming a β,γ-double bond. Therefore, a series of *S*-(4-chlorophenyl) 3-aryl-3-hydroxypropanethioates (I*a*–I*g*, Table I) was prepared and tested for activity *in vitro* against several selected bacterial species.



Scheme I

DISCUSSION

Chemistry—The title compounds were prepared by the following reaction sequence (Scheme I). The appropriately substituted benzaldehyde (II*a*–II*g*) was reacted with the zinc complex (III) formed by ethyl bromoacetate and zinc under the conditions of the Reformatsky reaction (6). The resulting crude ethyl 3-aryl-3-hydroxypropanoates (IV*a*–IV*g*) were hydrolyzed directly with alcoholic potassium hydroxide solution to yield the 3-aryl-3-hydroxypropanoic acids (V*a*–V*g*, Table II). The hydroxy acids were coupled with 4-chlorobenzenethiol (VI) using dicyclohexylcarbodiimide (VII) in dichloromethane to yield the desired products. All thiol esters showed a strong OH peak at 2.8–3.0 μm in their IR spectra (mineral oil mull).

Biological Activity—The propanethioates were screened *in vitro*