# THE FORMATION OF ACETYLCODEINE FROM ASPIRIN AND CODEINE PHOSPHATE

by

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# INTRODUCTION

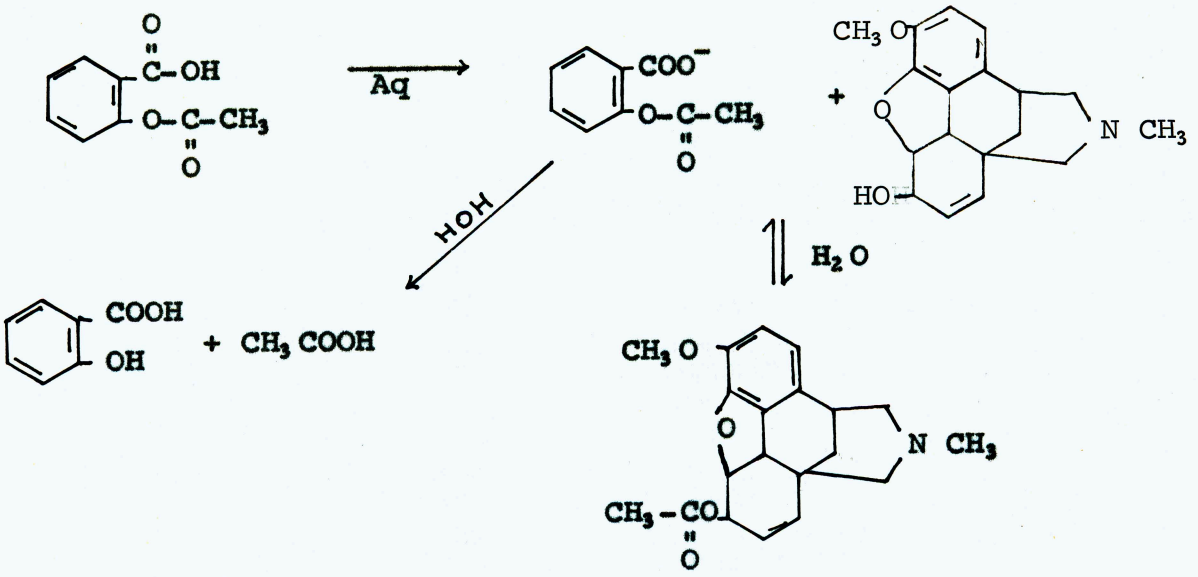
For the more efficient analgesic action, relaxation and sedation, a combination of aspirin, caffeine, phenacetin, and codeine phosphate has often been prescribed. The preparation of compressed tablets containing the above ingredients, however, has been rather a problem to many of the manufacturers, as the prepared tablets on aging become spotted and colored. Busse and Patel (1) have studied that the addition of powdered sugar or the mixture of powdered sugar and heavy magnesium oxide prevents the formation of spots and color in the tablets prepared from aspirin and codeine phosphate. Reports of the interaction of aspirin with other drugs have only recently begun to appear in the literature. Troup and Mitchner (2) reported that phenylephrine underwent acetylation in tablets containing aspirin. Under accelerated conditions, the mono-, di- and triacetylated products were formed. Even at 24$^0$ the secondary amine group was found to be acetylated to the extent of 14% after 34 months of storage. Jacobs, Dilatush, Weinstein, and Windheuser (3) in a study of capsule formulation containing aspirin and codeine phosphate observed that acetylcodeine was found but apparently only at elevated

temperatures in the presence of moisture. No acetylcodeine was detected in commercial samples stored for 32 months at room temperature. These capsules were prepared in such a manner that the total moisture present was less than 0.2%.

Schwartz and Amidon (4) recognized the possibility that aspirin might react with amino groups of proteins. More recently, Koshy et al (5) indicated the possibility of an interaction between aspirin and acetaminophen (APAP) in pharmaceutical preparations.

Although there is a wealth of published data about the kinetic investigation of hydrolysis of acetylsalicylic acid in the presence of accompanying substance and stabilizers in aqueous solution, there seem to have been no earlier attempts to ascertain the mechanism and kinetics of the reaction. The present report is concerned with results of studies designed to determine the rate and mechanism of formation of acetylcodeine in a mixture of codeine phosphate and aspirin.

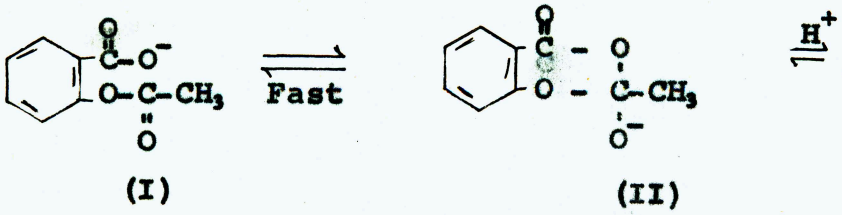
In aqueous solution, since water is a weak but effective nucleophile, aspirin undergoes relatively rapid hydrolysis (6). In the synthesis of acetylcodeine (7) codeine may react with anhydric ions. On the other hand, due to the hydrolysis of acetylcodeine (8), an equilibrium system may be expected as scheme I.



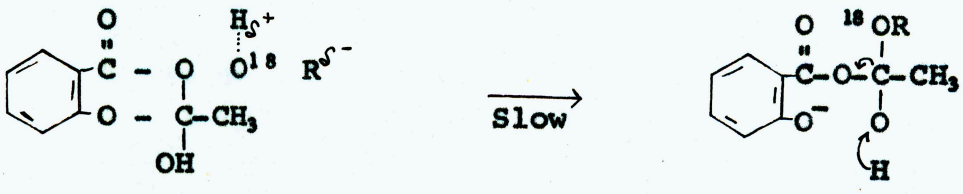

Scheme I

Formation of acetylcodeine probably results from intermolecular attack from the neighboring carbonyl group of aspirin. The reverse reaction may be due to the same mechanism and present in low concentration of aspirin.

In the solvolysis of acyl esters of salicylic acid, Garrett (9), consistent with the kinetic dependences (10), has evidenced a more probable mechanism as scheme II.

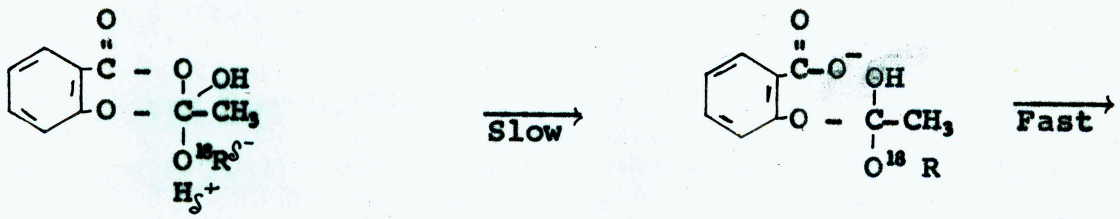


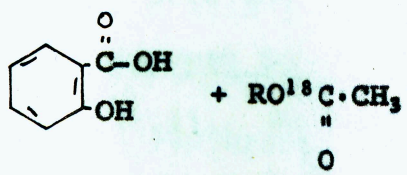

(I) (II)




(III) (IV)

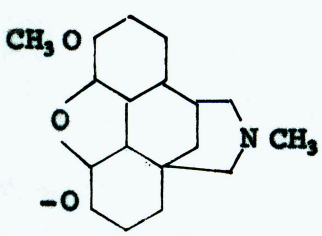
or by



Scheme II

R =



The presence of the anionic form of aspirin (I) is consistent with their argument that cyclization to (II) is favored by the carboxylation ion being more nucleophilic than carboxyl.

The present investigation was designed to determine whether the postulated reaction would occur and to establish the rates and products of the system. This was identified by thin-layer plate and analyzed by partition column (3).

## EXPERIMENTAL

### Equipment and Reagent

A Cary model 14 reading spectrophotometer was utilized for the spectrophotometric determinations.

All chemicals used were of U.S.P. or reagent grade.

### Analytical Procedures

Thin-layer Chromatography - plate - A 0.25 mm. layer of Silica Gel G (E. Merck, Darmstadt) was applied to the plates. The plates were air dried for 10 minutes and then heated in an oven for 45 minutes at 120°. The plates were then stored in a desicator until used.

Solvent System - (a) Chloroform-acetone-diethylamine, 5:4:1 (11). (b) Chloroform-methanol, 10:1.

Spray Reagent - One milliliter of 37% formaldehyde dissolved in 30 ml. of sulfuric acid (12).

### Procedure and $R_f$ Values

Spot the equivalent of 100 mcg of the alkaloid base

and develop over 15 cm. Dry the plate and spray with the reagent. Both codeine and acetylcodeine appear as purple spots. For nondestructive spraying, use distilled water to locate the compounds.

| | Solvent | |
|---|---|---|
| $R_f$ Values | (a) | (b) |
| Acetylcodeine | 0.7 | 0.95 |
| Codeine | 0.4 | 0.60 |

## Synthesis of Acetylcodeine (6)

1 gm of codeine phosphate with 2 ml acetic anhydride heated in oil bath up to 130°C for six hours. Extracted with chloroform and recrystallized from acetone and petroleum ether. Evaporate the mother liquid for three times and get yellowish-white crystals. If recrystallized from ether would get very good crystals. Identified thin-layer plate and the Δ melting point at 129-130°C.

## Determination of Acetylcodeine in Degraded Sample

Adjusted a 4% aqueous solution of citric acid monohydrate U.S.P. to pH 3.5 with 1 N sodium hydroxide. Mixed 4.5 ml of this solution with 7.5 Gm of acid-washed Celite 545 (Johns-Manville Corp.) and packed into a 200 x 25 mm chromatography tube previously plugged with glass wool. Top the Celite layer with a pledget of glass wool.

## Kinetic Procedure

Added 17 mg of codeine phosphate (0.02M) mixed with

0.726 gm of aspirin (2M) in 2 ml volumetric flask in different buffer solution. 1 N and 0.01 N hydrochloric acid solutions used as pH 1 and pH 2.2 buffering solutions. 0.1 N and 1 N sodium hydroxide solution used as pH 4 and pH 5 buffering solutions.

Sealed the volumetric flask and put in 80°C oil bath for reaction. At intervals, volumetric flasks were withdrawn and reacted with about 30 ml of 1 N sodium bicarbonate to transfer the mixture from the volumetric flask into separatory funnel. After shaking with 20 ml of chloroform, transferred the organic phase to the prepared column. Set a 100 ml volumetric flask as a receiver beneath the column. Performed two additional chloroform extractions of the sodium bicarbonate layer, adding each, in turn, to the column. Added sufficient water-saturated chloroform to the column to bring the eluate to 200 ml. Determined acetylcodeine in the eluate spectrophotometrically using its absorbance at 286 mμ. (A 1% of acetylcodeine = 44).

## RESULTS AND DISCUSSION

Due to the relatively fast hydrolysis of aspirin, a large excess concentration of aspirin is needed. As shown in Figure 1, the reaction is pH dependent. A plot of log ($ACOD_\infty - ACOD_t$) against time (where $ACOD_\infty$ is the concentration of acetylcodeine at infinite time, and $ACOD_t$ is the concentration of acetylcodeine at any time t) will yield a straight line. This shows it is an apparent

first order reaction dependent on the concentration of codeine in excess concentration of aspirin. The pH range studied was limited to that where acetylcodeine would not be rapidly hydrolyzed.

The pH-rate profile of acetylcodeine as shown in Figure 2 is similar to the hydrolysis of acetylsalicylic acid (aspirin) and the solvolysis of acyl esters of salicylic acid. It is apparently that the rate-determining step is the attack of the nucleophile on the proposed unchanged cyclic intermediate IV in scheme II. The codeine molecule being bulkier than the water molecule attacks the aspirin less strongly and hence the rates of reaction are slower than for the simple hydrolysis.

Table I is a tabulation of the observed values of the rate constants for the formation of acetylcodeine as a function of pH.

TABLE I

Effect of pH on the Rate of Formation of Acetylcodeine

| pH | $k_{obs}$ $hr^{-1}$ |
|---|---|
| 1 | $3.8 \times 10^{-1}$ |
| 2.2 | $2.67 \times 10^{-1}$ |
| 3.5 | $2.56 \times 10^{-1}$ |
| 4 | $7.1 \times 10^{-1}$ |
| 5 | 4.0 |

The data in Table I is plotted in Figure 2. The equilibrium value for the concentration of acetylcodeine is also highly

pH dependent as shown in Figure 3 and apparently follows a similar profile to that of the pH profile of the reaction which would indicate the probability that the aspirin anion is the reactive species and probably interacting with the protonated codeine. Based on this assumption, one would expect to find a linear relationship between the aspirin anion concentration and the observed reaction rate. In this system this was not observed and possibly may be due to the fact that the secondary reaction of the solvolysis of aspirin may be interfering. However, such a dependence was found by Koshy et al (4) and indicates a linear relationship between the degradation rproducts of aspirin and the acetylation of APAP. At this point it is not possible to formulate an exact mechanism nor to calculate a theoretical profile due to the complexity of the reaction. If the reaction simply involved the interaction of the protonated codeine with the aspirin anion, the pH would approximate a normal titration curve rather than going through a minimum and increasing as the pH falls below 3.

The commercial importance of this reaction is self-evident since numerous aspirin-codeine complexations are marketed both in tablet and in capsule form. Fortuitously, the minimum in the profile is at approximately 3.1 which is the normal pH of aspirin in a saturated solution. Consequently, most of the products are self-buffered to

the most stable pH. The reaction is only evident when the products are exposed to conditions of high humidity and temperature.

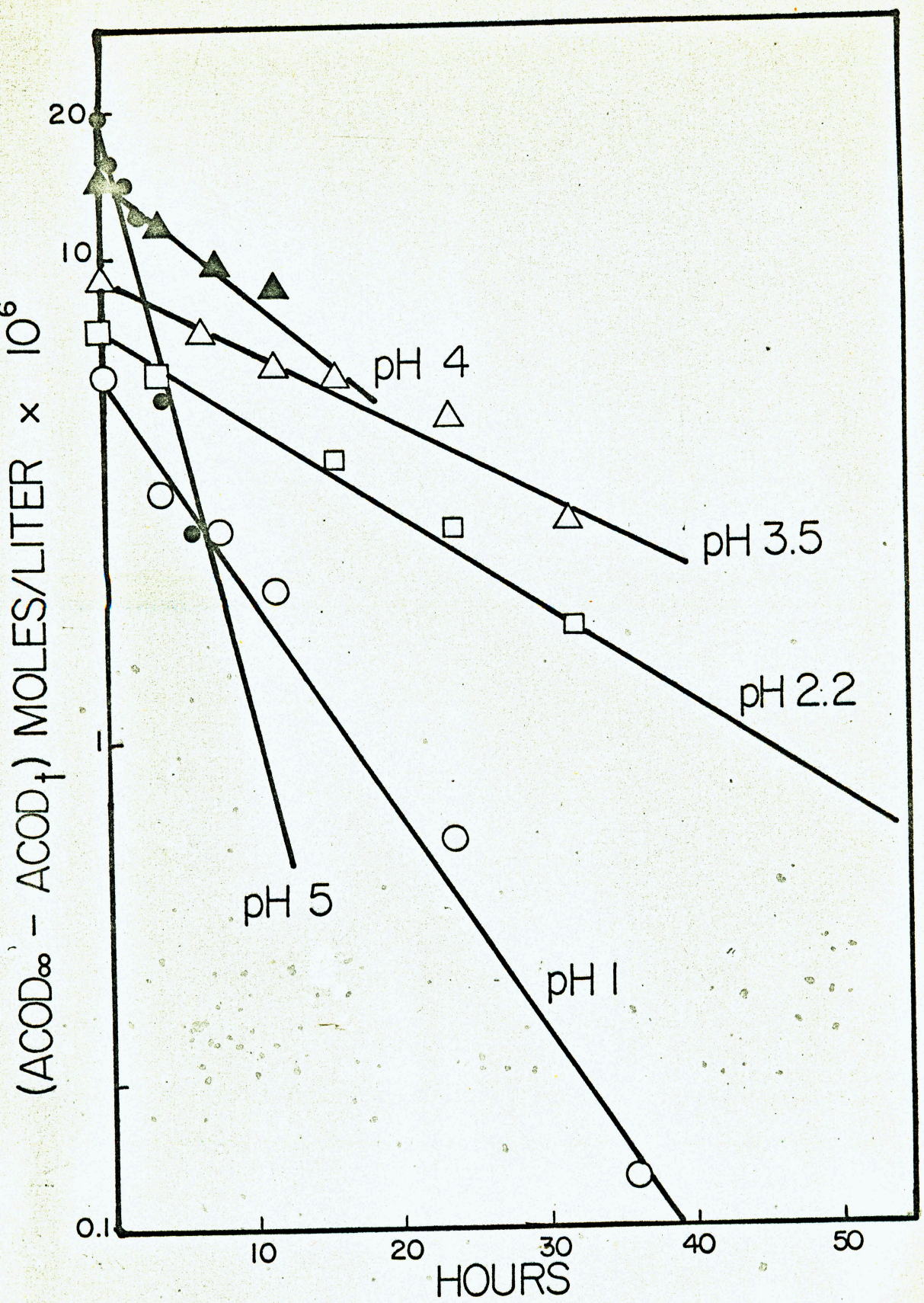



Fig. 1. Typical first order approach to equilibrium for the formation of acetylcodeine at 80°C.

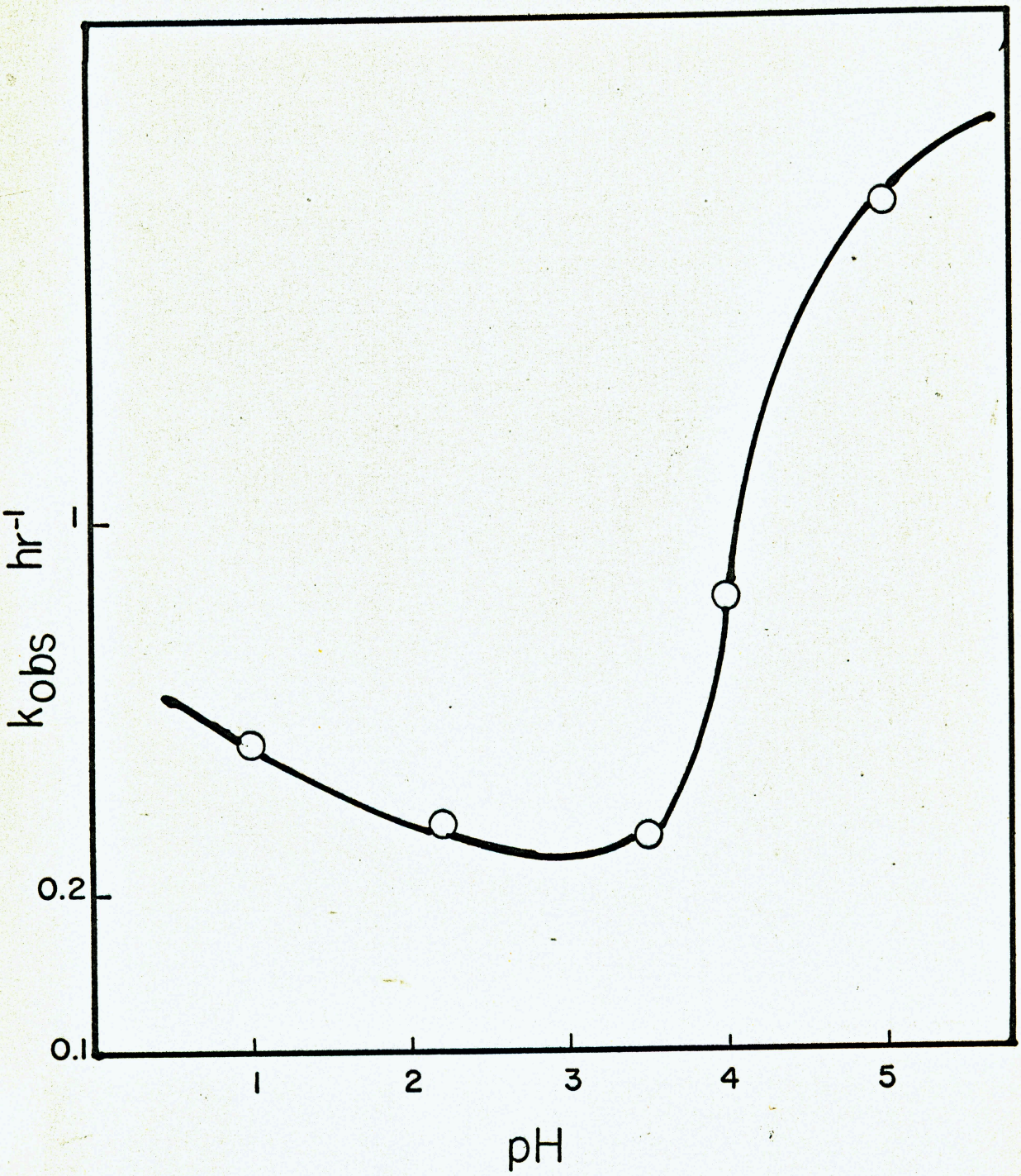



Fig. 2. The pH-rate profile of the apparent first order formation of acetycodeine at 80°C.

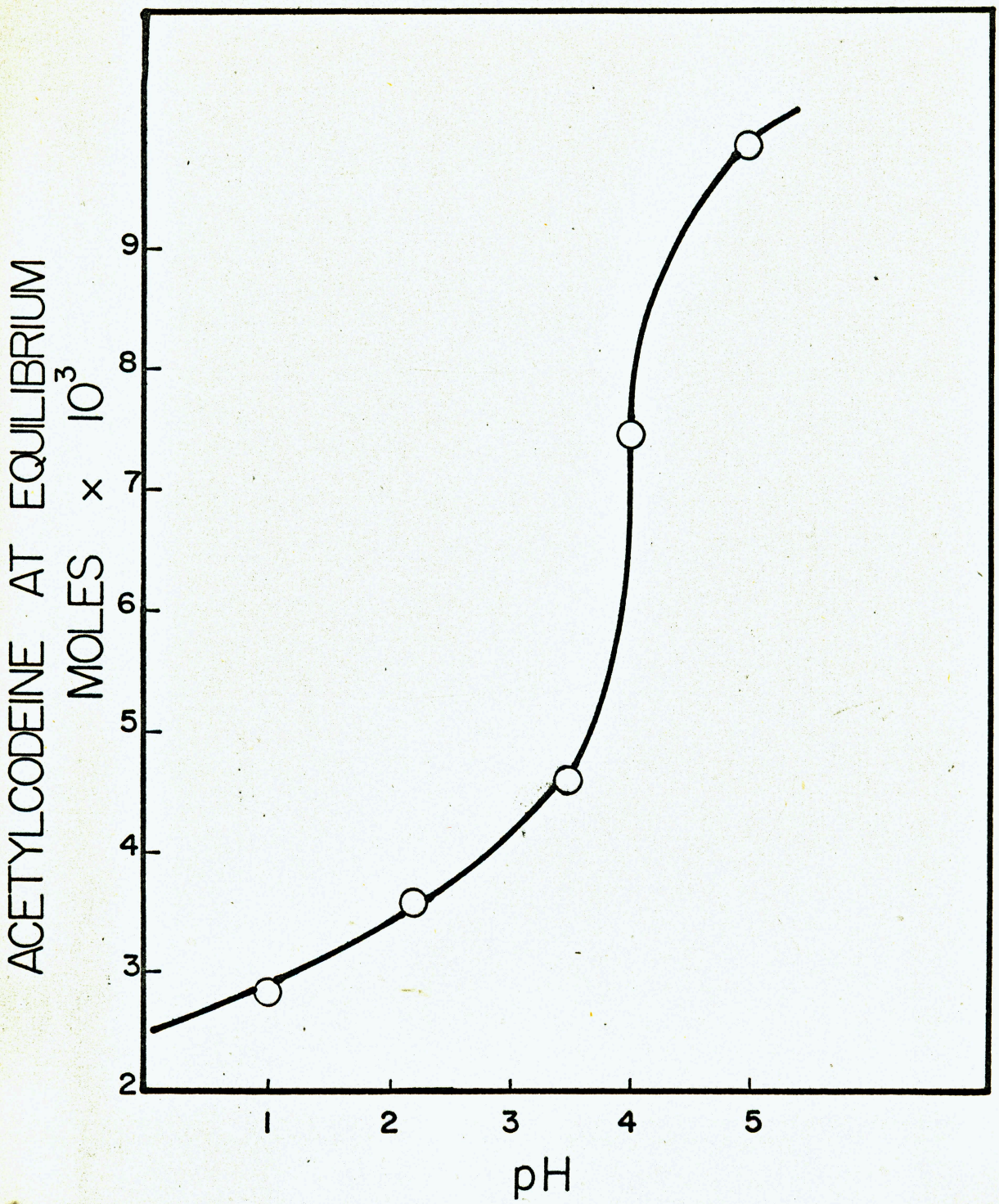



Fig. 3. Plot of the formation of acetylcodeine in equilibrium vs pH value (codeine = 0.02M, aspirin = 1M, T = 80°C.).

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APPROVED_____

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DATE_____