The Rearrangement of Codeine to Dihydrocodeinone*

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A study was made of the factors affecting the catalyzed rearrangement of codeine to dihydrocodeinone in acidic aqueous medium. A maximum yield of about 50 per cent of pure dihydrocodeinone was obtained. Certain provisional conclusions concerning the course of the reaction are discussed.

IT HAS been claimed in several German patents (1) that codeine can be isomerized to dihydrocodeinone in 70–95 per cent yields by means of a noble metal catalyst in an acidic aqueous or in an alcoholic medium.

There is a certain vagueness in the experimental descriptive sections of the German patents concerning reagent concentrations. It is also not quite clear whether the weight of crude or of recrystallized product was used as a basis for yield calculation. We have therefore examined the conditions of this rearrangement rather closely. In no case did we achieve yields higher than ca. 50 per cent in an individual experiment.[1,2]

When several attempts to rearrange codeine in alcoholic medium failed to give evidence of any reaction whatsoever, we abandoned this approach completely;[3] all rearrangements reported here were performed in acid medium.

Early in this investigation it became evident that a reliable method of determining the quantity of pure dihydrocodeinone formed in each run would have to be developed before variations in reaction conditions could be evaluated. Recrystallization of the crude product from alcohol (1) did not give dihydrocodeinone meeting the standards of New and Nonofficial Remedies (6), and in addition left varying amounts in mother liquors. Likewise recrystallization of crude dihydrocodeinone-sodium bisulfite and subsequent liberation of the purified alkaloid (7) was not satisfactory. The procedure finally adopted is described in the Experimental section; it was reasonably rapid and completely reproducible. All yields given in this report are based on results obtained by that evaluation procedure.

EXPERIMENTAL AND RESULTS

Table I is a summary of our most significant exploratory experiments. Individual runs or groups of runs will be cited in illustration of the conclusions we reached concerning the effect upon the yield of product of systematic changes in the reaction conditions (Procedure 1).

Procedure 1

In all cases 30.0 Gm. of codeine (anhydrous basis), 12.5 Gm. of catalyst A,[4] and 200 cc. of acid solution comprised the reaction mixture. After completion of the reaction under the conditions cited in Table I, the mixture was filtered, the catalyst washed with dilute acid, and the combined acid solutions made alkaline with sodium hydroxide to *p*H 10 and extracted with a total of 875 cc. of benzene. The benzene extracts were washed with water and then stirred with 50 cc. of 38% aqueous sodium bisulfite for one hour The precipitated dihydrocodeinone-sodium bisulfite was removed by filtration, air-dried, and evaluated by the procedure described below.

Acid Strength.—Runs 1–4 demonstrate that a strong acid is necessary for successful rearrangements.

Acid Concentration.—Run 5 leads to the conclusion that, provided a strong acid is used, the concentration of acid may be varied considerably without great effect upon the yield.

Temperature.—Run 4 *vs.* run 6 illustrates that the rearrangement is best conducted at reflux temperature.

Atmosphere.—In runs 7 and 8, nitrogen and hydrogen, respectively, were bubbled through the reaction mixture; the effect in both cases was deleterious.

Stirring.—Run 9, in which stirring was used, gave poor results. All other runs were done without stirring.

Time.—Run 10 illustrates that a considerable proportion of the rearrangement has occurred within the first twenty minutes of reflux. It is definitely advantageous, however, to continue the reaction beyond one hour.

On the basis of the above findings, the reaction conditions were standardized (Procedure 2) and the study restricted to an evaluation of the effects of changes of catalyst. As seen in Table II, these changes most profoundly influenced the yield.

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* Received May 23, 1951, from the Research Laboratory of the New York Quinine and Chemical Works, Inc., Brooklyn, N. Y.

† The suggestions and criticisms of Dr. W. G. Bywater, S. B. Penick and Co., are gratefully acknowledged.

[1] Similar results were evidently obtained by Rapoport, *et al.* (2). In a private communication Dr. Rapoport has informed us that he does not intend to publish the results of his study of this rearrangement.

[2] Since the submission of this manuscript, there has appeared an abstract of a Japanese paper [*J. Pharm. Soc. Japan*, **62,** 352(1942); *Chem. Abstr.*, **45,** 5167(1951)] which claims that codeine is rearranged to dihydrocodeinone in 75–79% yields using 10% palladium black as catalyst, 6% hydrochloric acid as medium, a temperature of 50–80°, and a current of hydrogen.

[3] The one exception was the unexpected finding that when codeine is heated with Raney nickel in toluene containing cyclohexanone (3), it is rearranged to dihydrocodeinone in 42% yield. Like Findlay and Small (3) we had investigated this reaction in an attempt to prepare codeinone which could then have been hydrogenated to dihydrocodeinone (4, 5).

[4] This catalyst was 5% palladium on activated charcoal, lot No. 860, Baker & Co., Newark, N. J.

TABLE I.—REARRANGEMENT OF CODEINE TO DIHYDROCODEINONE: CATALYST CONSTANT

Run No.	Acid Species	 Vol. (Cc.)	T., °C.	Time, Hr.	Alkali-Sol. Products, %[a]	Yield of Dihydrocodeinone, %
1	HOAc	10.8	Reflux	1.25	18.0	0.91
2	H_3PO_4	4.0	Reflux	1.25	17.3	0.52
3	HCl	15.3	Reflux	1.25	26.0	44.4
4	H_2SO_4	5.0	Reflux	1.25	17.5	47.0
5	H_2SO_4	10.0	Reflux	1.25	17.5	43.2
6	H_2SO_4	5.0	70	1.25	13.6	35.1
7[c]	H_2SO_4	5.0	90–93	3	14.6	33.8[b]
8[d]	H_2SO_4	5.0	Reflux	1.25	14.9	38.0
9	H_2SO_4	5.0	Reflux	1.25	15.0	36.1
10	H_2SO_4	5.0	Reflux	0.33	15.7	32.1

[a] Weiss, U., and Weiner, N., *J. Org. Chem.*, **14**, 194(1949) report the isolation of thebainone.
[b] Slow stream of hydrogen bubbled through reaction mixture throughout rearrangement.
[c] Product had to be twice purified over alumina.
[d] Slow stream of nitrogen bubbled through reaction mixture throughout rearrangement.

Procedure 2

The reaction mixture, consisting of 30.0 Gm. of codeine (anhydrous basis), 5.0 cc. of concentrated sulfuric acid, 195 cc. of water, and the quantity and type of catalyst indicated in Table II was heated under reflux without stirring for one and one-quarter hours. The isolation of product, etc., followed Procedure 1.

Quantity of Catalyst.—Runs 11 and 12 show that either increasing or decreasing the quantity of catalyst has a deleterious effect upon the yield obtained in run 4. The increase in the quantity of catalyst was associated with a significant increase in the amount of alkali-soluble products formed.

Concentration of Metal on Carrier.—Runs 13 and 14 demonstrate that an increase in the concentration of noble metal on the same carrier results in a decrease in yield. There was, surprisingly, no increase in the extent of formation of alkali-soluble products. See reference in footnote *a* to Table I.

Nature of Noble Metal.—Platinum, at least in our hands, gave poorer results (run 15) than palladium, and the addition of a small amount of platinum to a good palladium catalyst (run 16) likewise was harmful. Ruthenium, on the other hand, gave excellent results (run 17).

Activity Number.—We could find no correlation between the efficiency of a catalyst as measured by its performance in a hydrogenation and its ability to catalyze the rearrangement of codeine.

Bulk of Catalyst.—The results of several runs favored the conclusion that a bulky catalyst was desirable. Run 21 was made with a dense (i. e., *not* bulky) catalyst.

Evaluation of the Dihydrocodeinone-Sodium Bisulfite

A representative sample (15.0 Gm.) was suspended in 15 cc. of water in a 250-cc. beaker. Ninety cubic centimeters of ethylene chloride was added, stirring was started, and 15 cc. of concentrated ammonia was run in slowly. After ten minutes of stirring, the mixture was transferred to a separatory funnel and the layers separated. The aqueous solution was further extracted with two 45-cc. portions of ethylene dichloride. The combined organic extract was washed with water and dried over anhydrous sodium sulfate.

A column of activated alumina[5] 0.75 in. in diameter and 6 in. high was wetted with dry ethylene dichloride. Then the ethylene dichloride solution of the alkaloids was passed through by gravity, followed by 200 cc. of fresh dry solvent. The combined effluents were made to 400 cc. and a 25-cc. aliquot was evaporated to dryness; the residue was dried at 110° for two hours and weighed.

Let x = weight in Gm. of the dihydrocodeinone in 25 cc.; y = total weight in Gm. of the dihydro-

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[5] Alumina F-20, Aluminum Corporation of America, was used.

TABLE II.—EFFECT OF CATALYST VARIATIONS UPON YIELD

Run No.	Catalyst Metal, %	 Carrier	 Gm.	 Lot No.[a]	 Activity No.[b]	Yield of Dihydrocodeinone, %
4	Pd (5)	C	12.5	860	915	47.0
11	Pd (5)	C	6.25	860	915	32.3
12	Pd (5)	C	25.00	860	915	34.0
13	Pd (10)	C	12.5	[c]	..	24.1
14	Pd (15)	C	4.17	423	355	35.1
15	Pt (5)	C	12.5	514	785	<10.5
16	Pd (5)	C	12.0	860	915	35.3
	Pt (5)	C	0.5	514	785	45.3
17	Ru (5)	C	12.5	363A	..	
18	Pd (5)	C	12.5	845	965	36.3
19	Pd (5)	C	12.5	388	820	35.6
20	Pd (5)	C	12.5	380	465	33.3
21	Pd (5)	C	12.5	425	..	24.9

[a] Baker and Co., Newark, N. J.
[b] Supplied by the manufacturer and denotes the cc. of hydrogen absorbed in five minutes in the hydrogenation of double-distilled nitrobenzene in glacial acetic acid at room temperature using 500 mg. of catalyst. *Cf.* Hoffmann, *et al.* (8).
[c] Prepared in this Laboratory by the method of Organic Syntheses (9).

codeinone-sodium bisulfite. Then 3.56 xy is the % yield of dihydrocodeinone in the run.

Attempts to Dehydrogenate Dihydrocodeine to Dihydrocodeinone

Using 5% Palladium-on-Charcoal.—In a 100-cc. three-necked flask equipped with mercury-sealed stirrer, thermometer, and reflux condenser was placed 5.65 Gm. of dihydrocodeine dihydrate, an equal weight of 5% palladium-on-charcoal, and 20 cc. of xylene. The mixture was heated first to drive off water of hydration and then under reflux for four and one-half hours. It was cooled and filtered. The filtrate was shaken for thirty minutes with 17 cc. of a saturated aqueous solution of sodium bisulfite. No precipitate formed. The aqueous layer was separated and made alkaline. The precipitated gum was removed, dissolved in acid, and reprecipitated, yielding 5.34 Gm. of dihydrocodeine dihydrate.

Using Copper Bronze.—Dihydrocodeine dihydrate (5.60 Gm.) was dissolved in 100 cc. of diisopropylbenzene and heated under reflux for three hours with 1.0 Gm. of copper bronze. The mixture was cooled, filtered, and diluted with benzene to a volume of 135 cc. The filtrate was shaken for one hour with 8 cc. of 38% sodium bisulfite. After chilling, the lower layer was separated, made alkaline, and thoroughly extracted with chloroform. The chloroform solution was evaporated to dryness; the residue, 0.92 Gm., did not form an oxine and was therefore not dihydrocodeinone.

From the organic layer 4.50 Gm. of nonketonic alkaloid was recovered in the usual manner.

DISCUSSION

The catalyzed isomerization of codeine to dihydrocodeinone appears to be a complex process involving more than one mechanism. The mixture at the end of a run contains a multiplicity of products. The following conclusions and hypotheses are consistent with the facts:

1. The reduction of codeine to dihydrocodeine by the hydrogen absorbed on the catalyst is *not* the first step of the reaction. Dihydrocodeine is not dehydrogenated to dihydrocodeinone under "codeine rearrangement conditions" nor indeed under more vigorous conditions (palladium-on-charcoal in hot xylene; copper bronze at elevated temperatures).

2. The dehydrogenation of codeine to codeinone is a plausible first step, followed by:

(*a*) Reduction of codeinone to dihydrocodeinone (5).

(*b*) Transformation of a portion of the codeinone in the acidic medium to phenolic products (3).

(*c*) Hydrogenolysis of the ether bridges of codeinone and dihydrocodeinone, respectively, by means of H_2/Pd. We have found, for example, that dihydrocodeinone under "codeine rearrangement conditions" is converted to the extent of about 15 per cent into alkali-soluble products.

3. The formation of dihydrocodeine as a by-product,[6] probably by reduction of a portion of the original codeine by means of H_2/Pd, precludes the possibility that intramolecular transfer of hydrogen from the—CHOH group of codeine to the double bond or the oxygen bridge is the sole operating mechanism.

4. The efficacy of the catalyst as a dehydrogenating rather than a hydrogenating aid seems critical. Unfortunately the isolated dehydrogenation of codeine to codeinone has not yet been achieved. (*Cf.* footnote 3 and literature citations therein.)

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(8) Hoffmann, A. N., *et al.*, *Ind. Eng. Chem.*, **40**, 1708 (1948); *ibid.*, **41**, 1683(1949).

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[6] Isolated in this Laboratory previously from the reaction mixture.

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REMINGTON MEDAL AWARD

The Remington Medal, Pharmacy's highest award, will be presented to Dr. Hugo H. Schaefer at a dinner to be held in his honor on Tuesday evening, December 11, in the Grand Ballroom, Waldorf-Astoria Hotel, New York City.

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