A Convenient Laboratory Preparation of Ethylmorphine Hydrochloride, U. S. P. XIII*

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A procedure is described for preparing ethylmorphine hydrochloride in 90 per cent yield.

THE SYNTHESIS of ethylmorphine hydrochloride meeting pharmacopeial standards involves:

(*a*) Ethylation of morphine.
(*b*) Isolation and purification of ethylmorphine, including removal of unconverted morphine.
(*c*) Conversion of ethylmorphine to its hydrochloride.
(*d*) Purification of the hydrochloride.
(*e*) Recovery and re-use of alkaloidal material left in mother liquors.

Step *a* has been effected by a variety of reagents. A brief summary of the more important ethylation methods reported before 1932 is given in Small's monograph (1); no new ones have appeared since that date. We have found that ethyl bromide, introduced for this purpose by Mering (2), is, in spite of its volatility (b. p. 38°), very satisfactory. We have used ethanolic potassium hydroxide in the reaction mixture rather than the more troublesome ethanolic sodium ethoxide.

A description of the details of the remaining operations (steps *b* to *e*) has not appeared in the patent literature. The process recommended by Schwyzer (3) involves proceeding from crude ethylmorphine to purified ethylmorphine and then converting the latter to its hydrochloride. (It is not indicated whether or not this hydrochloride is sufficiently pure to meet official specifications.) The procedure described below requires fewer steps; the hydrochloride produced passes all U. S. P. XIII tests.

The yield data that have been previously reported are incomplete. Mering (2) claims an 85–90 per cent yield of *crude* ethylmorphine. Schwyzer (3) states that 85–90 per cent of *purified* ethylmorphine is obtained, exclusive of the quantity of morphine recovered. However, our interpretation of the data obtained at Merck, Darmstadt (4), where, apparently, a process very similar to the one described by Schwyzer (3) was employed, indicates that the yield of satisfactory product was 68 per cent based upon the total morphine charged and 79.4 per cent based upon the net morphine consumed (morphine charged minus morphine recovered). In several series of experiments, each comprising three successive runs, we have obtained a minimum yield of 90 per cent of final product based upon net morphine consumed. The data for one such series are given in Table I.

EXPERIMENTAL

A saturated solution of potassium hydroxide pellets, U. S. P., in absolute ethanol[1] was prepared in advance and assayed, by titration, for alkali concentration.

Ethylation.—One of the side necks of a 2-liter three-necked flask was fitted with a Claissen type adapter.[2] The assembly was now provided with a mercury-sealed stirrer, a 24-inch condenser protected by a calcium chloride tube, a thermometer to read the internal temperature of the reaction mixture and a 500-cc. dropping funnel. In the flask were placed 44.54 Gm. (0.156 mole) of anhydrous morphine,[3] 0.2 Gm. of zinc dust, 0.4 Gm. of anhydrous sodium sulfite, and 600 cc. of absolute ethanol.[1] Then sufficient ethanolic potassium hydroxide was added to provide 0.168 mole (an 8% excess) of alkali.[4] The mixture was stirred at room temperature until virtually all the morphine had dissolved. A solution of 20.42 Gm. (0.188 mole, a 20% excess) of ethyl bromide in 100 cc. of ethanol[1] was added rapidly. The mixture was heated under reflux for three hours.

Change of Solvents.—The reaction mixture was allowed to cool to about 50°, the condenser was set for distillation, and heating was resumed. In the course of about one and a half hours 1165 cc. of warm dry toluene[5] was allowed to run into the flask while simultaneously a mixture of alcohol and toluene was distilled out. The displacement of alcohol by toluene was considered to be complete when the vapor temperature reached 90°. By this time 1165–1170 cc. of distillate had been collected.

Recovery of Morphine.—The reaction mixture was cooled to 60–80° and transferred to a separatory funnel. It was shaken with two 40-cc. por-

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[1] Denatured alcohol, Formula 3A, was used.
[2] Ace Glass Inc., Catalog "40," item 5055.
[3] The sample used weighed 46.93 Gm. and was 94.90% pure.
[4] E.g., 45.3 Gm. of alcoholic potassium hydroxide assaying 3.707 milliequivalents of KOH per gram of solution.
[5] In subsequent runs of a series, part or all of this toluene contains recovered ethylmorphine.

tions of 5% aqueous potassium hydroxide and then with 100 cc. of water. The combined aqueous solutions were extracted once with 25 cc. of toluene; the latter was added to the main toluene solution.

The aqueous solution was acidified with acetic acid, boiled to remove traces of toluene, charcoaled, and filtered. The filtrate was cooled in an ice bath. Morphine was precipitated by the dropwise addition, with stirring, of concentrated ammonia to a *p*H of about 10.

Isolation and Purification of Ethylmorphine.—The toluene solution at 60–80° was shaken with three 165-cc. portions of 0.5 *N* H_2SO_4 and with one 25-cc. portion of water. The combined aqueous solutions were brought to *p*H 5. Three grams of $NaHSO_3$ was added and the solution was concentrated to one-half its original volume. During the final one-half hour of heating, 2 Gm. of Nuchar was also included. The solution was filtered hot, placed in a separatory funnel, cooled to 60–80° and covered with 150 cc. of toluene. Forty per cent sodium hydroxide solution was added, with intermittent shaking, until the *p*H was about 10. The layers were separated; the alkaline solution was extracted twice more with 100-cc. portions of toluene. The combined toluene solutions[6] were washed once with 25 cc. of water and then dried over anhydrous Na_2SO_4.

Precipitation of Crude Ethylmorphine Hydrochloride.—The filtered toluene solution[7] was chilled to 10°. A 10-cc. portion was removed and set aside. The remainder was stirred vigorously while to it was added a few drops of a solution of 12-cc. concentrated HCl in 460 cc. of dry acetone. The addition was interrupted and the oily precipitate was rubbed until it crystallized. Then the dropwise addition of the HCl solution was resumed and continued until the mixture became slightly acid to Congo red paper. The 10 cc. of solution that had been set aside was now stirred in.[8]

The mixture was refrigerated at 10° overnight. The crystals were removed by filtration and slurry-washed twice with 150 cc. of an acetone-toluene mixture (8 parts acetone: 5 parts toluene by volume). The washings were combined with the mother liquor. The crude ethylmorphine hydrochloride[9] was air-dried in the dark.

Recovery of Ethylmorphine.—The acetone-toluene solution was distilled at atmospheric pressure through an 8-inch Vigreux column in order to strip the acetone. This operation was considered to be complete when the vapor temperature reached 90°. The toluene solution was cooled to 60–80° and shaken with 100 cc. of 10% NaOH. The toluene layer is used in a subsequent run in lieu of a portion of the toluene needed to displace the alcohol at the conclusion of the ethylation.

Yield Data.—Table I summarizes the data obtained in three successive runs.

Table II presents the same data in terms of a materials balance for the three runs as a unit.

Ethylmorphine Hydrochloride, U. S. P. XIII.—Ten grams of crude ethylmorphine hydrochloride (from Run C) was dissolved in 40 cc. of boiling water and made slightly acidic to Congo red paper by the addition of a few drops of 3% HCl. Then 0.05 Gm. of $NaHSO_3$ and 0.2 Gm. Nuchar were added. The mixture was boiled for one-half hour—during which time the volume was allowed to decrease—and filtered hot. The charcoal was washed with a small

[6] When the toluene solution had a purplish cast, as happened occasionally, it was also washed once with a dilute solution of sodium hydrosulfite.

[7] In subsequent runs of a series a toluene solution containing recovered ethylmorphine was added at this point.

[8] The *p*H of 0.5% solutions of several lots of commercial ethylmorphine hydrochloride was found (M. Russo, N. Y. Q. Control Laboratory) to lie between 3.3 and 3.7.

[9] In a number of cases this "crude" product satisfied U. S. P. purity requirements. A recrystallization is recommended, however, in order to improve the color stability and to insure uniform acceptability.

TABLE I.—ETHYLATION OF MORPHINE: YIELD DATA

Run	Morphine Input—Wt., Gm.	Morphine Input—A. M. A.[a] Content[b]	Crude Ethylmorphine Hydrochloride—Solid, Gm.	Crude Ethylmorphine Hydrochloride—Ethylmorphine Content,[b] Gm.	Crude Ethylmorphine Hydrochloride—In Mother Liquor as Alkaloid, Gm.	Recovered Morphine—Solid, Gm.	Recovered Morphine—A. M. A. Content[b]	Recovered Morphine—In Mother Liquor as A. M. A.[d]
A	46.93	44.54	40.32	32.30	Into B	9.05	7.60	0.20
B	46.93	44.54	45.33	35.67	Into C	7.97	6.42	0.53
C	46.93	44.54	48.03	38.45	1.83[c]	8.85	7.26	0.07

[a] A. M. A. = anhydrous morphine alkaloid.
[b] Assays by N. Y. Q. Control Laboratory.
[c] Duplicate assays by K. S. Ellner and Walter Smith.
[d] Assays by N. Y. Q. Plant Laboratory.

TABLE II.—ETHYLATION OF MORPHINE: MATERIALS BALANCE[a]

	Input	Output	
Morphine	133.6 Gm. (100%)	As solid crude ethylmorphine hydrochloride	96.84 Gm. (72.48%)
		As recovered ethylmorphine	1.67 Gm. (1.25%)
		As recovered morphine (solid)	21.28 Gm. (15.93%)
		As recovered morphine (in solution)	0.80 Gm. (0.60%)
		Loss	13.0 Gm. (9.7%)
		Total	133.6 Gm. (100%)

[a] All alkaloid is expressed in terms of anhydrous morphine.

volume of boiling water; the washings were added to the filtrate. The *p*H was re-adjusted. The solution was stirred and chilled to induce rapid crystallization, and finally refrigerated for fifteen hours at 5–10°. The crystals were removed by filtration and slurry-washed with 10 cc. of ice water. After air-drying in the dark, the ethylmorphine hydrochloride (7.12 Gm.) met all U. S. P. XIII purity tests.

A materials balance made around this recrystallization step indicated that there had been no loss of alkaloid.

The ethylmorphine hydrochloride mother liquor is made alkaline and extracted with three portions of toluene. The toluene solution is added, in a subsequent run, to the solution from which crude ethylmorphine hydrochloride is to be precipitated.

SUMMARY

A procedure is described in detail for ethylating morphine with ethyl bromide in alcoholic medium. The replacement of ethanol by toluene at the conclusion of the ethylation, permits ready removal of unchanged morphine and further purification of the ethylmorphine in few steps. The addition of an acetone solution of hydrochloric acid to a toluene solution of ethylmorphine precipitates the alkaloid hydrochloride, which, as such, or after one recrystallization from water, meets U. S. P. XIII purity standards.

In a series of consecutive runs involving appropriate recycling of material, the yield of ethylmorphine hydrochloride, based upon morphine that has entered the reaction, is 90 per cent.

REFERENCES

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(2) Mering, U. S. Pat. 629,264, July 18, 1899.
(3) Schwyzer, J., "Die Frabikation pharmazeutischer und chemisch-technischer Produckte," Julius Springer, Berlin, 1931, pp. 374–6.
(4) Office of the Publication Board Reports, P. B. L. 84,957, p. 2732.

Toxicological Studies on Synthetic Glycerin*

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Acute and prolonged studies have failed to show any differences in the toxicity of natural and synthetic glycerin. The acute toxicities in mice following intravenous and oral administration are reported. Pathological changes in rats are compared after treatment for six months with natural and synthetic glycerin.

GLYCERIN, a trihydric alcohol, was discovered by Scheele in 1783 but was not used in pharmacy until many years later when it was employed as an emollient for retaining moisture on surfaces having a tendency to dry and crack. It first appeared in the third edition of the United States Pharmacopoeia, which became official in 1850. Today the use of glycerin is widespread and millions of pounds are consumed annually in the pharmaceutical industry alone. Lesser (1) has reviewed the many formulas where it is employed. Other uses include the manufacture of cigarettes, cosmetics, explosives, liqueurs, printing inks, liquid soaps, and lubricants.

Glycerin has been obtained for the most part as a by-product from the manufacture of soaps and fatty acids. During the war when large quantities were essential in the manufacture of explosives, other glycols were substituted in pharmaceuticals where possible. None seemed to be as universally acceptable as glycerin. It now appears that the use of detergents is increasing and if the manufacture of soaps declines, the supply of natural glycerin may become inadequate. The development of a process on a commercial scale for the production of synthetic glycerin will alleviate the necessity of finding substitutes.

Before synthetic glycerin can be used in products designed for human consumption, it must be shown to contain no harmful impurities. The toxicity of natural glycerin has been studied by numerous workers including Deichmann (2), von Oettingen (3), and Holck (4). Hart (5) could find no difference in the toxicity of natural and synthetic glycerin following oral administration of single doses to rats. We have attempted to compare the acute and chronic toxicities of the two products.

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