Table III—Significance Level of Treatment and Covariate on Pupil Dilation for the Seven-Digit Task at 2 hr

Seconds	Covariate: Number Correct Responses	Main Effect: Drug Treatment
6	0.090	NS[a]
7	0.028	NS
8	0.160	0.263
9	0.142	NS
10	NS	NS
11	0.280	0.041
12	0.174	0.131
13	NS	NS

[a] NS = not significant.

diameter tended to level. Thus, the lack of significance during the nine-digit task of this experiment was attributed to processing overload. The subjects of both the control and treatment groups began to overload during the 11th sec of the experiment, which rendered further pupillary dilation impossible (23).

The maximum difference between the control and placebo groups was observed at the 11th sec, immediately following the recitation of the last digit. Kahneman *et al.* (24) demonstrated that pupils may continue to dilate following random-digit memory tasks as subjects continue to work on the regrouping of stored information. This fact was substantiated by Peavler (9), who demonstrated that maximum dilation occurred 1–2 sec following stimulation. Therefore, the most significant differential measures were observed at the point where maximum dilation occurred without overload. The differences quickly vanished following the 12th sec, representing a lessening of cognition activity and pupillary dilation.

Variability in measurements was expected. The effects of hippus, eyelid closure, fatigue, and other sources contributed to the variance. Also, blood levels of diazepam are considerably variable at 1 and 2 hr following an oral dose (16). Furthermore, the experiment did not include controls for anxiety levels, which contribute to the response to diazepam (25). Future applications of the cognitive task technique may enhance sensitivity if blood levels and psychological state are evaluated.

The results supported the hypotheses. The group treated with diazepam did not dilate to the degree of the placebo group in response to the seven-digit cognitive task. Additionally, drug administration reduced the ability of the subjects to recall the seven randomized digits.

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Impurities in Drugs II: Meperidine and Its Formulations

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Abstract □ Three lots of meperidine hydrochloride, seven lots of meperidine tablets, and 41 lots of meperidine injectables were examined for impurities by TLC. Impurities found were ethyl 1-benzyl-4-phenyl-4-piperidinecarboxylate, methyl 1-methyl-4-phenyl-4-piperidinecarboxylate, ethyl 1-ethyl-4-phenyl-4-piperidinecarboxylate, and three unidentified compounds. Not all impurities were found in every lot of drug investigated, and none of the impurities exceeded a concentration of 1% of the meperidine present.

Keyphrases □ Meperidine—TLC analyses of impurities in bulk drug and dosage forms □ TLC—analyses, impurities in meperidine bulk drug and dosage forms □ Impurities—in meperidine bulk drug and dosage forms, TLC analyses □ Narcotic analgesics—meperidine, TLC analyses of impurities in bulk drug and dosage forms

Impurities in drugs and their formulations may originate as intermediates or by-products during synthesis of the drug substance or as products of degradation during formulation or storage of the finished product, or they may result from drug–excipient interactions. To obtain adequate information on the number and level of impurities

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Table I—Impurities in Meperidine and Its Formulations

Brand	Form	Dosage	Impurities					
						Unidentified		
			I (R_f 0.75)	II (R_f 0.60)	XI[a] (R_f 0.39)	R_f 0.56	R_f 0.33	R_f 0.25
A	Bulk drug	—	1.0	0.25	—	Tr	—	Tr
A	Bulk drug	—	1.0	Tr	—	—	Tr	—
A	Tablet	50 mg	—	Tr	—	Tr	Tr	Tr
A	Tablet	50 mg	Tr	0.25	+	Tr	0.5	Tr
B	Tablet	50 mg	1.0	0.25	+	Tr	0.5	Tr
B	Injection	75 mg/ml	—	0.5	—	Tr	—	—
C	Injection	75 mg/ml	—	1.0	—	Tr	0.5	—
C	Injection	100 mg/ml	1.0	0.5		Tr	Tr	—
E	Injection	10 mg/ml	0.5	Tr	—	—	—	—
E	Injection	50 mg/ml	—	Tr	—	Tr	—	—
F	Injection	50 mg/ml	—	Tr	—	Tr	—	—
F	Injection	50 mg/ml	—	0.25	+	Tr	0.5	—
I	Injection	75 mg/ml	1.0	0.25	+	Tr	0.25	—

[a] Detected but not quantified.

in pharmaceutical products, it is desirable to examine a substantial number of formulations and drug substances. Chromatographic techniques, geared to the detection of compounds structurally related to the drug, are most suitable for this work. A study of impurities in imipramine and desipramine showed the presence of several compounds related to the drug (1). This paper reports a study of the impurities in meperidine and meperidine formulations.

Meperidine was first synthesized (2) by condensing mechlorethamine with benzyl cyanide, followed by hydrolysis and esterification of the resulting nitrile. Several alternative methods have been developed (3–6). A number of qualitative TLC methods for the determination of meperidine have been published (7–13), but only two (12, 13) deal with impurities in meperidine.

BP (14) monographs for pethidine hydrochloride (meperidine) and its formulations specify a TLC limit test of not more than 1% for unidentified related substances. The USP (15) does not contain specifications for impurities in meperidine hydrochloride.

EXPERIMENTAL

Materials—All drugs and dosage forms were obtained directly from the manufacturers. Meperidine hydrochloride[1], *N*-benzyliminodiacetic acid[2], hexamethylphosphoramide[3], thionyl chloride[4], lithium aluminum hydride[5], sodium amide[6], 10% palladium-on-charcoal[7], absolute ethanol[8], and hydrogen chloride gas[9] were obtained commercially. All other solvents were analytical grade.

Precoated silica gel GF (20 × 20-cm, 0.25-mm) TLC plates[10], 60–200-mesh silica gel for column chromatography, and nylon columns[11] were used. A gas chromatograph[12] equipped with flame-ionization detectors was used with 1.8-m × 0.63-cm o.d., U-shaped glass columns packed with 5% phenylmethyl silicone (OV-25) coated on acid-washed, dimethylchlorosilane-treated, high performance Chromosorb W[13] (100–120 mesh).

Standard Solutions—Two aqueous solutions were prepared, each containing 20 mg of meperidine hydrochloride/ml. To the first solution was added 0.05 mg/ml; to the second was added 0.1 mg/ml of each of the hydrochloride salts of ethyl 1-benzyl-4-phenyl-4-piperidinecarboxylate (I) and ethyl 1-ethyl-4-phenyl-4-piperidinecarboxylate (II). Aliquots of 5 ml of each solution were made basic with 0.5 ml of concentrated ammonium hydroxide and shaken with 2 ml of ether for 15 min. The standard solutions in ether contained 50 mg of meperidine/ml and either 0.125 or 0.250 mg of I and II/ml.

TLC System—The solvent system consisted of ethyl acetate–cyclohexane–methanol–dioxane–water–concentrated ammonium hydroxide (50:50:20:10:1:1). Filter paper-lined TLC tanks were equilibrated with the solvent system for 15 min prior to use. Spots were visualized using UV light at 254 nm and by spraying with dilute potassium iodobismuthate solution.

Extraction from Tablet Formulations—An amount of powdered tablet equivalent to 100 mg of meperidine hydrochloride was weighed into a 10-ml screw-capped culture tube[14] and extracted by shaking[15] for 30 min with 5 ml of distilled water. The aqueous extract was made basic with 0.5 ml of concentrated ammonium hydroxide solution and extracted with 2 ml of ether by shaking for 15 min. Aliquots of the ether layer were applied directly from the culture tubes to the TLC plates.

Extraction from Injectable Formulations—An amount equivalent to 100 mg of meperidine hydrochloride was diluted to 5 ml with distilled water in a screw-capped culture tube, made basic, and then extracted. An aliquot was applied to the TLC plate as already described.

Extraction from Drug Substances—Aqueous solutions were prepared to contain 100 mg of meperidine hydrochloride in 5 ml of distilled water and extracted in the same manner as injectable formulations.

Isolation of Impurities—Meperidine base (3 g) was extracted from Formulation C, 100 mg/ml (Table I), which had been determined by preliminary TLC investigation to contain the largest number and quantities of impurities. The base was generated from bulked injectable formulations, which were made alkaline with concentrated ammonium hydroxide and extracted with 5 × 100 ml of ether.

The ether was evaporated under vacuum. The isolated base was then dissolved in 5 ml of chloroform and adsorbed onto the top of a dry-packed silica gel column, prepared from 200 g of 60–200-mesh silica gel that had been equilibrated with 15% water and packed into a 0.03 × 1-m nylon column by the method of Loev and Snader (16). The silica gel was not equilibrated with the developing solvent as reported in a later publication (17), because the separation at the various bands was adequate when water alone was used.

The solvent system used to elute the drug and impurities on the column was the same as that used for TLC. The location of each compound on the column was established by removing small portions of the silica gel through holes cut into the nylon tube every 1.27 cm and eluting these aliquots with ethanol directly onto a TLC plate. The components were visualized as described for the TLC system.

Sections of the column were excised, and the impurities were eluted by shaking with successive aliquots of ethanol until a drop of the eluate failed to respond to the test for the basic drug substance when examined on a TLC plate. The various fractions were evaporated under vacuum and further purified by preparative TLC with the same solvent system. The residues isolated from the TLC plate were determined to consist of a single component by rechromatographing aliquots with the same TLC system.

[1] USP reference standard.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Eastman Kodak Co., Rochester, N.Y.
[4] J. T. Baker Chemical Co., Phillipsburg, N.J.
[5] Alfa Products, Beverly, Mass.
[6] Fisher Scientific Co., Fair Lawn, N.J.
[7] Koch-Light Laboratories, Colnbrook, England.
[8] Consolidated Alcohols, Toronto, Canada.
[9] Matheson, Toronto, Canada.
[10] Brinkmann Instruments, Toronto, Canada.
[11] ICN Pharmaceuticals, Cleveland, Ohio.
[12] Bendix 2500, Aviation Electric, Montreal, Canada.
[13] Chromatographic Specialties, Brockville, Canada.
[14] Canlab Laboratories, Ottawa, Canada.
[15] Horizontal shaker, Eberbach Corp., Ann Arbor, Mich.

Prior to mass spectral analysis, a portion of the extract was further purified by GLC to remove contaminants originating from the silica gel. The injection port and detector block temperatures were 240°. The column temperatures were adjusted between 160 and 230°, depending on the retention time of the peak of interest. Fractions were collected in dry ice-cooled capillary tubes held over the exit tip of the flame-ionization detector at the retention time established for the compound of interest.

Collections were made, with the hydrogen flame extinguished, until a condensate was visible in the capillary tube. Samples thus collected were reexamined by TLC to ascertain that the compound consisted of a single component with chromatographic characteristics identical to those of the original material.

Screening for Impurities—Aliquots of 10 and 20 μl (0.5 and 1.0 mg, respectively) of the drug or formulation extracts were spotted on the silica gel GF TLC plates adjacent to 10- and 20-μl aliquots of the standard solutions. Impurities were estimated by comparison of the spot diameters and intensities to those of the corresponding spots from the standard solutions. In all cases, 10- and 20-μl aliquots of the aqueous phase prior to being made basic were applied to the chromatoplates to check for the presence of 1-methyl-4-phenyl-4-piperidinecarboxylic acid (III).

Syntheses—Scheme I illustrates the syntheses of the following compounds.

Diethyl N-Benzyliminodiacetate (IV)—A mixture of 45 g of *N*-benzyliminodiacetic acid (V), 39.7 g of concentrated sulfuric acid, and 2 liters of absolute alcohol was refluxed for 24 hr. The solution was concentrated to 500 ml, neutralized with sodium ethoxide, and evaporated to dryness. The residue was treated with ether, filtered to remove inorganic salts, and evaporated to dryness to yield 49 g (87%) of IV; IR (film): λ_{max} 1740 (ester carbonyl) and 3440 cm^{-1} (carboxylic hydroxyl was absent); PMR ($CDCl_3$): 73 (ethyl ester triplet) and 249 (ethyl ester quartet) Hz.

N-Benzylbis(2-hydroxyethyl)amine (VI)—Twenty grams of lithium aluminum hydride was slowly added to a stirred solution of 48 g of IV in 500 ml of dry tetrahydrofuran. The reactants were stirred at room temperature for 1.5 hr and hydrolyzed with 1.0 *N* NaOH until effervescence ceased. The mixture was filtered, and the filtrate was evaporated to yield 26 g (77%) of VI; IR (film): λ_{max} 3370 (hydroxyl) and 1740 cm^{-1} (ester carbonyl was absent); PMR ($CDCl_3$): 181 (hydroxyl protons) Hz (ethyl ester peaks were absent).

N-Benzylbis(2-chloroethyl)amine (VII)—Twenty-five grams of VI was refluxed with 38.9 g of redistilled thionyl chloride in 200 ml of dry chloroform for 1.5 hr. Ether was added to the cooled reaction mixture to induce crystallization. The yield of the hydrochloride salt of VII was 27 g (79%), mp (hydrochloride) 147° [lit. (2) mp 149°].

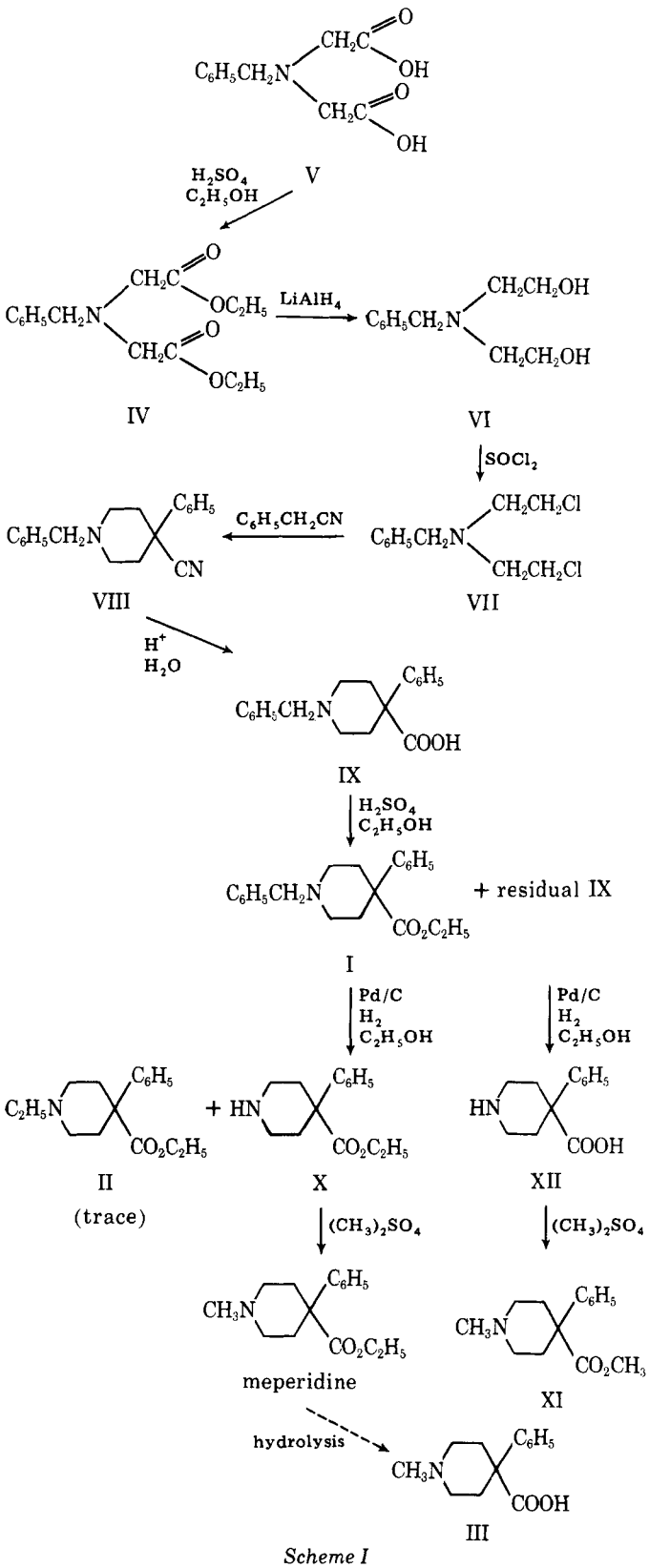
1-Benzyl-4-phenyl-4-cyanopiperidine (VIII)—A solution of 27 g of the hydrochloride salt of VII in 50 ml of water was made basic with concentrated ammonium hydroxide and extracted into 250 ml of toluene. The toluene was removed and dried with anhydrous sodium sulfate and subsequently mixed with 11.9 g of benzyl cyanide and 12 ml of hexamethylphosphoramide. To the stirred solution was slowly added 10.1 g of sodium amide suspended in 10 ml of dry toluene while the reaction temperature was kept below 10°.

After the addition was complete, the mixture was stirred for 3 hr at room temperature and then diluted with 250 ml of toluene. The organic phase was washed with 3 × 100 ml of water to remove the hexamethylphosphoramide and extracted with 3 × 100 ml of 10% HCl. The aqueous layer was made alkaline with sodium hydroxide and extracted with 2 × 50 ml of toluene. The toluene was dried and evaporated to yield 9.1 g (33%) of VIII, mp (hydrochloride) 255° [lit. (2) mp 259°].

Ethyl 1-Benzyl-4-phenyl-4-piperidinecarboxylate (I)—A solution of 9 g of VIII in 20 ml of 65% (v/v) aqueous sulfuric acid solution was heated at 130–140° for 2 hr. A 1-ml portion of the reaction mixture was removed and neutralized with 1 *N* NaOH, and the liberated base was extracted into 25 ml of chloroform to yield 1-benzyl-4-phenyl-4-piperidinecarboxylic acid (IX). The remainder of the reaction was cooled to 100°, and absolute ethanol was added continuously while distilling off the water–ethanol azeotrope. The rates of addition and distillation were balanced and continued for 24 hr.

The residue was poured onto ice, and the aqueous solution was washed with 2 × 25 ml of ether and then made basic with sodium hydroxide. The product was extracted into 2 × 25 ml of ether, and the ether was dried over anhydrous sodium sulfate and evaporated to yield 4.1 g (36%) of I. It gave a hydrochloride from ethanol–ether, mp 236° [lit. (2) mp 235–238°].

Ethyl 4-Phenyl-4-piperidinecarboxylate (X)—A solution of 1 g of the free base of I in 100 ml of absolute ethanol was hydrogenated at atmospheric pressure with 0.1 g of 10% palladium-on-charcoal catalyst until



Scheme I

no further hydrogen was absorbed (24 hr). The catalyst was filtered off, the solvent was evaporated, ethanolic hydrochloric acid was added, and the product was recrystallized from ethanol–ether to yield 0.3 g (41%) of the hydrochloride of X, mp 134–137°.

Ethyl 1-Ethyl-4-phenyl-4-piperidinecarboxylate (II)—A solution of 0.1 g of the free base of X in 10 ml of acetone was refluxed for 1 hr in the presence of 0.06 g of anhydrous potassium carbonate and 0.07 g of diethyl sulfate. The reaction mixture was cooled and filtered, and the

filtrate was evaporated under reduced pressure. The residue was dissolved in 25 ml of ether and washed with 2 × 25 ml of 2% potassium hydroxide and subsequently with 2 × 25 ml of water. The ethereal solution was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 0.08 g (71%) of II, which gave a hydrochloride from ethanol–ether, mp 169° [lit. (18) mp 171°].

Methyl 1-Methyl-4-phenyl-4-piperidinecarboxylate (XI)—A solution of 1 g of meperidine hydrochloride was warmed at 60° in 50 ml of 10 *N* HCl for 12 hr. Then the crystalline solid that separated was filtered off and washed with 2 × 1 ml of water and 3 × 25 ml of ether. The insoluble residue was established by IR and mass spectral analyses to be 1-methyl-4-phenyl-4-piperidinecarboxylic acid hydrochloride (III).

The carboxylic acid (0.7 g) was refluxed for 4 hr with 100 ml of dry methanol, which had been saturated with hydrogen chloride gas. The solvent was removed under vacuum, and the residue was recrystallized from methanol–ether to yield 0.5 g of XI hydrochloride, mp 212° [lit. (5) mp 201–202°].

RESULTS AND DISCUSSION

The TLC R_f values of meperidine, impurities found in formulations, and intermediates in Scheme I are given in Table II. The identities of I, II, and XI were established by TLC, GLC, and mass spectral comparisons to the corresponding authentic materials. TLC showed that a single ether extraction was sufficient for the complete removal of meperidine and its basic associated impurities from formulations. The presence of ether-insoluble impurities was determined by applying aliquots of the aqueous layer remaining after extraction to the TLC plates. No degradation of the drug or associated impurities was observed when extracts were subjected to two-dimensional TLC or when samples were applied to the TLC plates at intervals over 3 hr.

Three lots of meperidine hydrochloride, seven lots of tablets, and 41 lots of injectable preparations from nine manufacturers were examined for impurities. Examples of the products examined and the impurities found are listed in Table I. None of the samples contained III, a hydrolysis product of meperidine. The levels of those impurities not identified were estimated by assuming their TLC response to be equal to that of meperidine. Impurities stated to be present at trace amounts were approximately equal to the minimum detectable quantity established for the impurity or for meperidine.

Attempts to isolate the impurity at R_f 0.33, present in amounts comparable to other impurities, were unsuccessful, possibly because of its volatility. The concentration of XI could not be determined accurately in the presence of meperidine because it overlapped the tailing edge of the meperidine spot in all TLC systems investigated. However, XI was separated from the bulk of meperidine by the column procedure and purified by TLC.

The mechanism by which impurities I, II, and XI would form during synthesis by the routes described previously (2, 3) is not entirely clear. Grew (12) suggested that II and XI might form by an amino–ester exchange; however, the occurrence of I has not been reported previously. It is possible that I, II, and XI could arise as by-products of the synthesis shown in Scheme I. Compound I would be present if incomplete *N*-debenzylation occurred. Compound II may arise during catalytic debenzylation through interaction of the ethanol solvent normally employed, while XI would be produced from residual IX remaining after esterification. This material would then be debenzylated and subsequently methylated at both the nitrogen and carboxylic acid groups during methylation.

Table II—TLC Characteristics of Meperidine and Its Synthetic Intermediates and Impurities

Compound	TLC R_f[a]	TLC Detection Limit[a], μg
V	0.00	—
III	0.00	0.50
X	0.10	—
IX	0.20	—
XI	0.39	0.50
VI	0.42	—
Meperidine	0.47	0.25
II	0.60	0.25
IV	0.70	—
VIII	0.71	—
VII	0.73	—
I	0.75	0.25

[a] Determined on each substance applied separately to the chromatoplate.

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