plasticizers to the medical and para-medical professions.

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Synthesis of Tropine-Labeled Atropine II

Prototype Synthesis for the Preparation of Tropine-^{14}C and Atropine-^{14}C from Arabinose-^{14}C

By GILBERT C. SCHMIDT*, THOMAS E. ELING, JOHN M. McOWEN, and JOHN C. DRACH†

Prototype methods for the synthesis of tropines-^{14}C and tropine-labeled atropines are described. These compounds and the requisite labeled intermediates may be synthesized from arabinose-5-^{14}C or arabinose-UL-^{14}C. Yields for each step in the conversion of arabinose to succindialdehyde *via* 2,5-diethoxytetrahydrofuran have been determined. Predicted yields of 27 per cent atropine, based on starting pentose, were confirmed by synthesis of the alkaloid from 2 mmole quantities of arabinose. This procedure is the first published method for labeling atropine in the carbon skeleton of the tropine moiety.

FEW METHODS for selectively labeling atropine have been published. Labeled tropic acid has been synthesized by adaptations of Blicke's procedure (1), then converted to correspondingly labeled atropine by modifications of the Wolffenstein esterification (2). Using these methods, atropine has been labled with ^{14}C in the carboxyl position (3) and in the α-position (4) of the tropic acid moiety. Subsequent studies with the labeled alkaloids (5–9) have contributed much to an understanding of atropine metabolism, but the metabolic fate of the tropine moiety is not known.

The virtual absence of studies concerned with the metabolic fate of tropine indicates that suitably labeled compounds are not readily available for study. Randomly ^{14}C-labeled atropine has been biosynthesized (10) and atropine has been randomly labeled with tritium (11), but these compounds lack the desired specificity of labeling. Selective tritiation of tropine has been accomplished recently (12), but the heterocycle was converted to deptropine rather than atropine (13). *Datura metel* is known to incorporate 80–85% of the radioactivity from acetate-2-^{14}C into positions 2,3,4 of tropine (14, 15), but the exact position or positions of labeling are unknown. When *D. metel* is grown on acetate-1-^{14}C (14, 15) or *Datura stramonium* is grown on ornithine-2-^{14}C (16, 17), radioactivity is incorporated with stereochemical specificity into position 1 or position 5 of the tropine moiety. These biosynthetic compounds have not been available for metabolic studies and problems inherent in biosynthetic methods limit feasibility of this approach to tropine labeling. Standard synthetic methods for labeling the tropine moiety of atropine are needed, but few have been reported. Werner *et al.* (3), Fodor *et al.* (18), and Eling *et al.* (19) have used classical organic syntheses to obtain *N*-methyl-^{14}C-tropine and *N*-methyl-^{14}C-atropine, but these compounds are of limited value because the methyl carbon attached to the endo nitrogen bridge, rather than the carbon skeleton of tropine, is labeled. The need of practical methods for labeling the carbon skeleton of tropine is acute and the problem remains unsolved.

Three fundamental problems are encountered in the synthesis of tropine-labeled atropine: reproducibility of the esterification, feasibility of the Robinson condensation, and availability of labeled intermediates suitable for synthesis of succindialdehyde and acetone dicarboxylic acid, the

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key compounds in the Robinson condensation. The problems of condensation and esterification have been studied recently (20) and reproducible microsynthetic methods now are available. The present needs are for suitably labeled intermediates and microsynthetic methods for converting them to labeled succindialdehyde or labeled acetone dicarboxylic acid.

This communication presents, in detail, a prototype method for the synthesis of tropine-labeled atropine from arabinose.[1] The starting material is available in labeled forms suitable for the synthesis of tropine-1,5,6,7-^{14}C or tropine-1-^{14}C (or tropine-5-^{14}C), from which the correspondingly labeled atropines can be synthesized. Except for biosynthetic procedures, it is the first microsynthesis suitable for selectively labeling the carbon skeleton of tropine.

EXPERIMENTAL

Synthesis of Furaldehyde from Arabinose—Furaldehyde was synthesized from arabinose by a modification of Pervier and Gortner's method (22). In a 500-ml. round-bottom flask fitted for steam distillation, 300 ml. of 12% HCl was heated to 100° and 300 mg. arabinose[2] dissolved in the hot solution.[3] While heating with a heating mantle at a rate to maintain the vapor phase at 103.5–105.5°, steam was passed into the distilling flask and distillation continued until 1000 ml. of distillate had been collected.[4] At this point, single drops of distillate were tested with 2,4-dinitrophenylhydrazine solution[5] until the red precipitate characteristic of furaldehyde no longer appeared.[6] The entire solution was used, without concentration, for conversion of furaldehyde to furoic acid.

Conversion of Furaldehyde to Furoic Acid—Furoic acid was prepared from furaldehyde by a modification of Wagner and Simons' procedure (25). Furaldehyde from the previous step,[7] contained in a 2-L. beaker, was adjusted to pH 12 with saturated NaOH, cooled to 10°, and continuously stirred with a mechanical stirrer during the gradual addition of 0.3 Gm. $KMnO_4$ dissolved in 25 ml. water. The reaction mixture was boiled gently for 15 min.,[8] filtered, and the filtrate acidified with HCl. The acidified filtrate was concentrated *in vacuo* at 70° to a volume of 30 ml., then five times extracted with 50-ml. portions of diethyl ether. The ether solution of furoic acid was transferred to

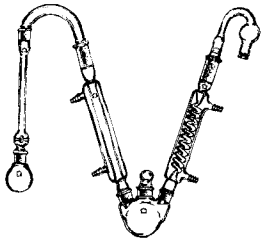


Fig. 1—Simplified decarboxylation apparatus.

a sublimation flask,[9] the solvent removed *in vacuo*, and the sublimation flask, containing the light tan product, dried for 2 hr. in a vacuum desiccator. After drying the flask was fitted with a cold finger containing dry ice–acetone and the furoic acid sublimed onto the cold finger by heating the flask for 30 min. at 15 mm. and 100°. The sublimates[10] were removed from the cold fingers with a small amount of absolute ether, the solvent was evaporated, and a residue of pure, white furoic acid obtained.[11]

Synthesis of Furan from Furoic Acid—Furoic acid was decarboxylated to furan by adapting for microsynthesis the method of Wagner and Simons (25). A simplified decarboxylation apparatus,[12] shown in Fig. 1 and constructed entirely of standard-taper microglassware,[13] was used. A 50-ml. three-neck flask was used as a receiving vessel. One opening of the receiver was fitted with a spiral water-cooled condenser, protected by a soda and lime tube. The second opening was fitted with a water-cooled straight condenser. The middle opening was fitted with a glass plug to permit access to contents of the receiver. The reaction vessel, a 5-ml. round-bottom flask, was fitted to the delivery end of an air-cooled condenser. Receiver and reaction assemblies were connected by a modified U-tube constructed of two adapters bent to the proper angles.

The receiver, containing a mixture of 5 ml. absolute ethanol and 20 ml. absolute diethyl ether,[14] was cooled to −40° and the temperature maintained at this level throughout subsequent steps. Furoic acid from the previous step,[15] 8.5 mg. cupric oxide, and 0.5 ml. water-free quinolin[16] were introduced into the reaction vessel and all joints sealed. The reaction vessel was heated on an oil bath until gas evolution became vigorous (about 200°) and the temperature gradually raised to 275°, at which point it was maintained for 15 min.[17] The resulting furan,

[1] A preliminary report was presented to the American Association for the Advancement of Science (21).

[2] Matheson, Coleman and Bell, Cincinnati, Ohio, m.p. 157–160°, used without further purification.

[3] In preliminary experiments to determine yields, 100–500 mg. arabinose was used. For conversion to tropanone, a minimum of 300 mg. arabinose is recommended.

[4] Complete distillation usually required 6–8 hr. and produced 1000–1250 ml. distillate. It is essential that the stated distillation range be maintained. At lower temperatures furaldehyde does not distil properly, and at higher temperatures decomposition of the product decreases yields.

[5] A standard solution of 2,4-dinitrophenylhydrazine, as described by Shriner *et al.* (23), was used in qualitative and quantitative precipitations.

[6] In quantitative studies to determine the yield for this step, the dinitrophenylhydrazone was isolated and weighed, m.p. 230°, after recrystallization from ethanol (24).

[7] In experiments to determine yields for this step, 0.2 ml. freshly distilled furaldehyde was dissolved in 1000 ml. water and treated as described.

[8] To insure complete precipitation of MnO_2.

[9] Of the design described by Werner (3), having a capacity of 250 ml.

[10] To obtain the last traces of furoic acid after the first sublimation, the flask was washed with ether to dissolve selectively any residual furoic acid. The solution was decanted into another sublimation flask, the solvent evaporated, and the residue sublimed as described previously.

[11] Melting point 130–132° without recrystallization.

[12] In the original apparatus there was a soda and lime trap between the two condensers, to remove CO_2 and water. In microsyntheses, the small quantities of furan produced were adsorbed on the soda and lime. The trap was, therefore, omitted from the reaction train.

[13] Microware, Kontes Glass Co., Vineland, N. J.

[14] Anhydrous conditions must be maintained.

[15] In experiments to determine yields for the conversion of furoic acid to furan, 190 mg. furoic acid was used routinely with the stated quantities of reagents. In other experiments, 5-Gm. quantities of furoic acid were used with corresponding increases in reagents.

[16] Quinolin must be water free and was redistilled immediately before use.

[17] At the stated temperature, quinolin refluxes about halfway up the air condenser. While heating from 200°–275°, furan began to distil into the receiving vessel. When larger quantities of furoic acid were used (5 Gm.), the resulting furan was purified by fractionally distilling at 31–32° and atmospheric pressure.

representing an 88% yield from furoic acid and a 70% yield from arabinose, was immediately converted to tetrahydrofuran, as described below.[18] The bromine number of furan was calculated from the difference in amounts of thiosulfate required to titrate blank and standard solutions.[19] Replicate determinations with known furan solutions gave bromine values of 460–470 mg. bromine per 100 mg. furan. To determine the furan yield in a particular synthesis, an aliquot of the diluted, glacial acetic acid solution of the product was assayed as just described. Furan production was then calculated on the basis of the previously determined bromine number for furan.[20]

Synthesis of 2,5-Diethoxytetrahydrofuran—Furan was converted to diethoxydihydrofuran and diethoxytetrahydrofuran by a micro modification of Fakstorp's (27) procedure. The solution of furan in ethanol and ether,[21] from the preceding step, was introduced into the reaction vessel,[22] cooled to −40° in a dry ice–acetone bath, and a solution of 0.08 ml. bromine in absolute ethanol[23] added, while stirring continually, at a rate to prevent a rise in temperature. Stirring was continued for 15 min. after adding all the bromine, the dropping funnel was replaced with an inlet tube and, while stirring, dry ammonia was bubbled into the reaction mixture until pH 6 was attained.[24] Stirring was continued until the color had disappeared, ammonia was again bubbled in to obtain a pH of 8, precipitated ammonium bromide removed by centrifugation, and the solution of 2,5-diethoxydihydrofuran concentrated to 10 ml.[25] The pale yellow solution of diethoxytetrahydrofuran was transferred to a micro hydrogenation apparatus,[26] using small volumes of absolute ethanol to transfer the last traces, and the volume finally adjusted to 50 ml. with absolute ethanol. With the magnetic stirrer in motion, three "micro spatelafuls" of freshly prepared Raney nickel[27] were added and a very slow[28] stream of hydrogen passed through the reaction mixture until reduction was complete.[29] Hydrogenation usually was complete in about 2 hr., at which time the catalyst was removed by centrifugation, leaving a colorless solution of diethoxytetrahydrofuran in ethanol.[30] The catalyst was washed with several 1-ml. portions of absolute ethanol and the washings combined with the previously obtained alcoholic solution of product.

Synthesis of Tropanone—Tropanone was prepared by the "standard" micro Robinson condensation previously described (20). Succindialdehyde was obtained *in situ* by removal of the solvent,[31] and was then condensed *in situ* with equimolar quantities of methylamine HCl and freshly prepared acetone dicarboxylic acid. The product was purified by micro sublimation and dried in a desiccator[32] before reduction to tropine.

Reduction to Tropine and Esterification with Tropic Acid—Tropanone was reduced to tropine,[33] converted to the hydrochloride and esterified with tropic acid,[34] as described previously (20).[35]

RESULTS AND DISCUSSION

The development of micro methods for the synthesis of tropine and for esterification of this heterocycle with tropic acid has made feasible the synthesis of tropine-labeled atropine. Atropine has been labeled in the bridge position of the tropine moiety by use of methylamine-^{14}C in the micro Robinson condensation, but methods for labeling the carbon skeleton of the tropine moiety have not been published. The feasibility of such labeling depends on on the availability of labeled Robinson intermediates

[18] The apparatus was allowed to cool to room temperature, then the last traces of product were washed from the condenser into the receiver. Receiver and contents were maintained at −40° until used in subsequent steps. In experiments to determine the yield of furan from furoic acid, 25 ml. of glacial acetic acid replaced the ether–alcohol mixture in the receiving vessel. After washing the condenser with a little glacial acetic acid, the solidified solution of furan in glacial acetic acid was allowed to liquefy and was then assayed as described.

[19] The bromine number of furan, defined as mg. bromine reacting with 100 mg. furan, was calculated as follows:

$$\frac{(\text{blank} - \text{sample})(N\ Na_2S_2O_3)(\text{mol. wt. } Br_2)(100)}{(\text{mg. furan in the known aliquot assayed})} = \text{bromine No. of furan}$$

[20] Using the previously determined bromine value of 460 mg. bromine/100 mg. furan, the furan contents of unknown samples were calculated as follows:

$$\frac{(\text{blank} - \text{unknown})(N\ Na_2S_2O_3) \times (\text{mol. wt. } Br_2)(100)\ (\text{dilution factor})}{460} = \text{mg. furan in total distillate}$$

[21] To determine yields of diethoxydihydrofuran and diethoxytetrahydrofuran from furan, 100 mg. pure furan was dissolved in a mixture of 20 ml. absolute diethyl ether and 5 ml. absolute ethanol.

[22] The reaction vessel was a 50-ml. three-neck flask that had been fitted with a thermometer, dropping funnel, and mechanical stirrer. Prior to use, the apparatus was dried by warming with a flame from a Bunsen burner.

[23] Bromine was dissolved in commercial, absolute ethanol, and a 1–2-ml. aliquot containing the stated amount of bromine was used. The alcoholic solution of bromine was cooled to −40° before addition to the cold furan solution.

[24] On bubbling in ammonia, ammonium bromide separated immediately. At pH 6 (Hydrion paper), the temperature had risen to −5° and was not permitted to rise above this level.

[25] To determine the yield of diethoxydihydrofuran from furan, the product from 500 mg. 5-Gm. furan was purified by fractional distillation at 69–72° and 5 mm. Fakstorp (27) reported b.p. 50–53° at 1 mm. Yield was determined by weighing the purified product.

[26] Available from Microware, Inc., Vineland, N. J. The apparatus was immersed in ice water and ice water was used to cool the "cold finger," to prevent evaporation of both product and reactant. Unless extreme care is exercised, losses occur by volatilization on passage of hydrogen.

[27] Raney nickel was prepared as described previously (20).

[28] It is essential that the flow of hydrogen be very slow to prevent losses of reactant and product by volatilization. It is probable that hydrogenation in a closed system, used in syntheses to be reported subsequently, would be equally effective and more convenient. This method was not, however, used in syntheses from arabinose.

[29] To test for completeness of reduction, a 1-ml. aliquot was removed and treated with 2,4-dinitrophenylhydrazine solution. A yellow precipitate of the succindialdehyde derivative indicated complete reduction, while an orange-red precipitate of the malaldehyde derivative indicated incomplete reduction.

[30] In experiments to determine the yield of 2,4-diethoxytetrahydrofuran, the product was acid-hydrolyzed to succindialdehyde, from which the bis-dinitrophenylhydrazone was prepared. The melting point (28) in semimicro and macro experiments was 260° without recrystallization and 272° on recrystallization from ethanol. In micro syntheses m.p. 272° was obtained without recrystallization.

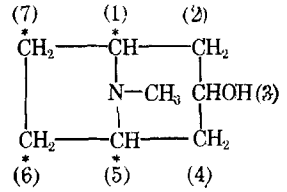
[31] Solvent was removed on the flash evaporator; succindialdehyde distilling at 78–80° and 20 mm. In experiments to determine succindialdehyde yields from diethoxytetrahydrofuran, the furan derivative was purchased from Beacon Chemicals, Cambridge, Mass., and was used without purification. In experiments to determine the dialdehyde yields from succinaldoxime, the oxime was prepared as described by Keagle and Hartung (28) and was recrystallized from water before use in the condensation.

[32] Tropanone yields were determined as the free base, after purification by micro sublimation, and as the picrate, m.p. tropanone 41–43°, m.p. tropanone picrate 220°.

[33] Because Raney nickel is extremely susceptible to poisoning, it was necessary to use highly purified hydrogen available in small cylinders, or to purify by washing the hydrogen obtained commercially in large cylinders.

[34] Nutritional Biochemicals, Cleveland, Ohio, m.p. 157–160°, used without further purification.

[35] Atropine determined gravimetrically and an aliquot converted to the picrate, m.p. free base 114–116°, m.p. picrate 174–175°. All melting points reported in this communication were determined with a Fisher-Johns melting point apparatus.

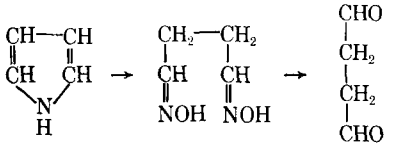


Tropine

other than methylamine. Starting with succindialdehyde, any or all of the indicated positions of tropine could be labeled, depending upon the labeling in succindialdehyde.

Succindialdehyde, the key intermediate for labeling positions 1,5,6,7 of tropine, has been prepared in a number of ways, many of which are not suitable for ^{14}C-labeling because of experimental conditions or because suitable starting materials are are not available. Among the potentially applicable procedures are preparation by ozonolysis of cyclooctadiene (29), oxidation and subsequent reduction of furan (30), preparation from pyrrole (28, 31), and synthesis by hydrolysis of 2,5-diethoxytetrahydrofuran (20, 32).

The authors initially prepared succinaldoxime from pyrrole, and the dialdehyde from this intermediate, as described by Keagle and Hartung (28).



Pyrrole Succinaldoxime Succindialdehyde

Using micro quantities of pyrrole, the expected 45% conversion to the intermediary dioxime was obtained. The purified dioxime was then converted to succindialdehyde, which was determined as the bis-dinitrophenylhydrazone. That the dioxime undergoes 90% conversion to the dialdehyde, as reported by Keagle and Hartung, was confirmed. When used in the Robinson condensation, the dioxime did not react to the same extent, as is shown in Table I. This difference in reactivity appears to account for the different yields reported by Keagle and Hartung (28) and by Werner *et al.* (3).

Because they obtained 90% conversion of succinaldoxime to the bis-dinitrophenylhydrazone of succindialdehyde, Keagle and Hartung assumed the same conversion to dialdehyde in the Robinson condensation.

Based on the calculated amount of aldehyde, 60% of theoretical tropanone yields were reported. Using the same method of calculation, the authors repeatedly confirmed the reported yields. In contrast, Werner *et al.* used a relatively large excess of dioxime and calculated tropanone yields on the basis of methylamine. Using the method of Werner and co-workers, the authors also obtained 70–75% tropanone yields from methylamine. Using 2,5-diethoxytetrahydrofuran as a source of succindialdehyde, and no excess of either reactant, 75% of theoretical tropanone yields were obtained. From these observations, it was concluded that an unpredictable excess of succinaldoxime is required in the Robinson condensation. Determination of the succindialdehyde as the bis-dinitrophenylhydrazone is not a reliable measure of the extent to which the oxime will react in the condensation.

TABLE I—COMPARISON OF TROPANONE AND SUCCINDIALDEHYDE YIELDS FROM PURIFIED SUCCINALDOXIME AND 2,5-DIETHOXYTETRAHYDROFURAN

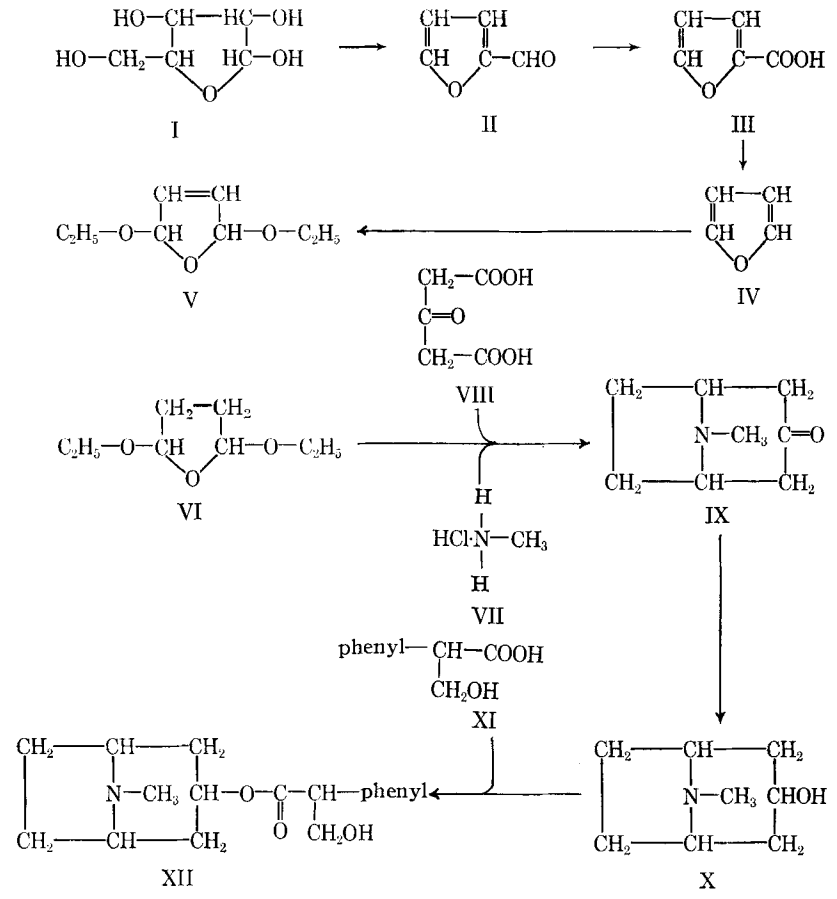
Source of Succindialdehyde	mmoles of Source Employed	Succindialdehyde[a] Yield, %	Tropanone[b] Yield, %
Succinaldoxime[c]	1.12	90 (89–91)	60 (58–62)
Succinaldoxime[d]	1.50	90 (89–92)	72 (70–75)
2,5-Diethoxytetrahydrofuran[e]	1.00	99.5 (99–100)	73 (70–75)
2,5-Diethoxytetrahydrofuran[e]	1.50	99.5 (99–100)	71 (68–74)
2,5-Diethoxytetrahydrofuran[e]	2.00	99.5 (99–100)	75 (74–77)

[a] Succindialdehyde was isolated and determined as the bis-dinitrophenylhydrazone, m.p. 278–279°. [b] Yields are tropanone, purified by microsublimation and melting at 41–43°; yields as the picrate, m.p. 220°, were 1–2% higher. [c] Tropanone yields based on calculated aldehyde production, as described by Keagle and Hartung (19); no excess of succinaldoxime. [d] Tropanone yields based on methylamine, using an excess of succinaldoxime, as described by Werner *et al.* (3). [e] Yields based on methylamine; equimolar quantities of methylamine, acetone dicarboxylic acid, and diethoxytetrahydrofuran were used in the Robinson condensation.

When the *N*-methyl carbon is to be labeled, poor conversion of pyrrole to the dioxime, the need to recrystallize this intermediate, and the requirement for an unpredictable excess of the purified oxime are disadvantages of little consequence. Circumstances are quite different if the resulting succindialdehyde is to be utilized as the instrument for ring labeling. The stated disadvantages then become a major concern and practically exclude pyrrole as a labeled precursor to radioactive succindialdehyde. As a result, 2,5-diethoxytetrahydrofuran was considered for use in the synthesis of labeled succindialdehyde.

Compared to pyrrole, the furan derivative proved to be a far superior source of succindialdehyde. Its use for this purpose has been reported in both chemical and patent literature, but it has not been used previously in the Robinson condensation, nor has the aldehyde been produced so simply as described in this communication. Most authors have hydrolyzed diethoxytetrahydrofuran with acid, in an atmosphere of nitrogen, and have removed the acid as the barium salt. Neither of these steps was necessary for use of this compound in the Robinson condensation. Direct conversion of the intermediate to succindialdehyde was effected by a very simple, rapid, *in situ* acid hydrolysis at room temperature. Derivatives of the resulting dialdehyde melted sharply and correctly without recrystallization. When used in the Robinson condensation, *in situ* hydrolysis obviated the need for isolation of an intermediate. No excess of diethoxytetrahydrofuran was required, the condensation proceeded smoothly, and reproducible 70–75% tropanone yields were obtained with 1 mmole or less of the aldehyde source.

The superiority of 2,5-diethoxytetrahydrofuran as a source of succindialdehyde led to development of the reaction sequence shown in Scheme I for its synthesis from commercially available labeled compounds.



Scheme I

For the proposed sequence, the steps from diethoxytetrahydrofuran (VI) to atropine (X) have been established by microsynthetic studies of the individual reactions (20). Diethoxytetrahydrofuran (VI) yields tropanone (IX) in 75% of theoretical quantities, conversion of tropanone to tropine (X) is essentially quantitative, and esterification of tropine with tropic acid (XI) produces atropine (XII) in 70–75% of theoretical yield. The predicted 49–53% yield of atropine from diethoxytetrahydrofuran has been confirmed repeatedly by microsynthesis of the alkaloid. Usefulness of the proposed method for labeling atropine therefore depends on the efficient conversion of arabinose to 2,5-diethoxytetrahydrofuran.

That arabinose (I) can be converted quantitatively to furaldehyde (II) was shown by Pervier and Gortner (22) during the development of a titrimetric assay for pentosans. Large volumes of distillate were required, but furaldehyde yields from either arabinose or xylose were quantitative. Bonner and Roth (33) prepared furaldehyde from xylose by essentially the same procedure, but did not isolate the intermediate furaldehyde. Direct oxidation with silver oxide gave 30% furoic acid (III), based on starting pentose. In contrast, Wagner and Simons (25) obtained "over 80%" furoic acid by permanganate oxidation of furaldehyde. Using the micro adaptations described under *Experimental*, the authors obtained 98% furaldehyde from arabinose and 83% furoic acid from furaldehyde. Observed and previously reported data are compared in Table II. These findings were confirmed by the direct conversion of micro quantities of arabinose to furoic acid. As shown in Table III, experimental yields were slightly below levels predicted from the individual steps. Based on these observations, the microsynthesis of furaldehyde (II) and furoic acid (III) from arabinose (I) was assumed to be practical. The efficiency of subsequent steps in the proposed sequence therefore became the key to tropine labeling.

For the conversion of furoic acid (III) to furan (IV), the catalytic decarboxylation of Wagner and Simons (25) was modified as described under *Experimental*. To determine efficiency of the conversion, micro quantities of furoic acid were decarboxylated, the product was trapped in glacial acetic acid, and the resulting solution assayed by a modification of Angelli's method (26). In parallel experiments, the acetic acid solution of furan was prepared directly from arabinose, then assayed. The data, shown in Tables II and III, confirm the findings of Wagner and Simons and establish the practicality of converting arabinose (I) to furan (IV).

The subsequent conversion of furan (IV) to the intermediate diethoxydihydrofuran (V) and to diethoxytetrahydrofuran (VI) was equally feasible.

TABLE II—COMPARISON OF OBSERVED AND REPORTED YIELDS FOR INDIVIDUAL STEPS IN THE CONVERSION OF ARABINOSE TO SUCCINDIALDEHYDE

Reaction	Ref.	Wt. of Starting Material	Yield for the Step Shown, %
Arabinose	[a]	500 mg.	98
	[a]	300 mg.	95
	[a]	100 mg.	98
	(22)	200 mg.	100
Furaldehyde	(33)	500 mg.	...
Furaldehyde	[a]	5.0 Gm.	83
	[a]	200 mg.	80
	(25)	25 Gm.	80
Furoic acid	(33)	...	30
Furoic acid	[a]	5.0 Gm.	88
	[a]	190 mg.	88
Furan	(25)	25 Gm.	90
Furan	[a]	5.0 Gm.	79
	[a]	500 mg.	76
	[a]	100 mg.	77
Diethoxydihydrofuran	(27)	36 Gm.	70
Diethoxydihydrofuran	[a]	5.0 Gm.	81
	[a]	100 mg.	79
	[a]	70 mg.	75
Diethoxytetrahydrofuran	(27)	79 Gm.	85
Diethoxytetrahydrofuran	[a]	1.0 Gm.	100
	[a]	150 mg.	99
	[a]	100 mg.	99
	[a]	75 mg.	99
	[a]	50 mg.	98
	(32)		100
Succindialdehyde	(27)	16 Gm.	30

[a] This report. [b] Yield is for conversion of xylose to furoic acid; the intermediate, furaldehyde, was not isolated.

TABLE III—PREDICTED AND OBSERVED YIELDS OF SUCCINDIALDEHYDE AND ITS PRECURSORS AND OF ATROPINE AND ITS PRECURSORS WHEN ARABINOSE IS USED AS A STARTING MATERIAL

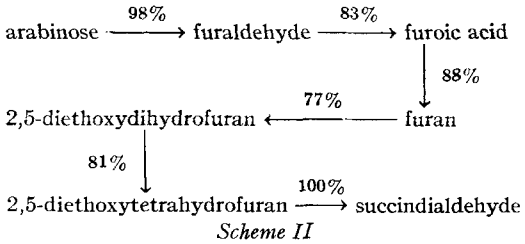
Compd. Synthesized	Observed Yields from Immediate Precursor, %	Yields Predicted from Individual Steps, %	Observed Yields from Arabinose, %
Furaldehyde	98	...	98
Furoic acid	83	81	70–73
Furan	88	71	70
2,5-Diethoxydihydrofuran	77	55	Not isolated
2,5-Diethoxytetrahydrofuran	81	45	50
Succindialdehyde	99.8	45	50
Tropanone	75	34	38
Tropine	98	33	34
Atropine	71–75	22–25	24

Yields for the individual steps were first determined with 5-Gm. quantities of furan and diethoxydihydrofuran. On isolation and purification of the dihydro compound, 77% of theoretical yields were obtained from furan. Conversion of the dihydro compound to the tetrahydro compound which was assayed by hydrolysis to succindialdehyde and isolation of the bis-dinitrophenylhydrazone, gave 81% of theoretical yields. In confirmatory, micro experiments furan was converted to diethoxytetrahydrofuran, without isolation of the intermediate. Yields for the direct conversion (70%) were higher than predicted from the individual steps (63%), a discrepancy that probably arose from losses during isolation and purification of the intermediate. Data for the conversion are in agreement with the findings of Fakstorp (27) and were confirmed by synthesis of 2,5-diethoxytetrahydrofuran from micro quantities of arabinose. The data, shown in Tables II and III, establish feasibility of these conversions and of the entire sequence from arabinose (I) to succindialdehyde. Establishment of this sequence simultaneously establishes the feasiblity of using labeled arabinose as an instrument for labeling tropine and the tropine moiety of atropine.

SUMMARY AND CONCLUSIONS

Previous work (20) has shown that the micro Robinson condensation is practical, that the reduction of tropanone to tropine is essentially quantitative, and that esterification of tropine with tropic acid gives 70–75% of theoretical atropine yields. In the present report, it has been shown that 2,5-diethoxytetrahydrofuran yields 75% tropanone when hydrolyzed *in situ*, employing a very simple procedure. Predicted yields of 49–53% atropine from 2,5-diethoxytetrahydrofuran have been confirmed by microsynthesis.

A reaction sequence for the production of diethoxytetrahydrofuran from arabinose has been proposed. Quantitative studies of each step in the sequence have yields for the individual steps shown in Scheme II.



Scheme II

Cumulative yields at each point in the sequence have confirmed yields for the individual steps. Validity of the sequence was finally established by the synthesis of 50% succindialdehyde and 37% tropine from arabinose. Additional verification was obtained by the synthesis of 26% atropine sulfate from 300-mg. quantities of arabinose.

Since arabinose-5-^{14}C and arabinose-UL-^{14}C are available commercially, the proposed sequence is a practical approach to the synthesis of tropine-1-^{14}C, tropine-1,5,6,7-^{14}C, and of atropines correspondingly labeled in the tropine moiety. Based on ^{14}C, 37% tropine and 26% atropine yields may be expected from arabinose-5-^{14}C, 29.6% labeled tropine and 20.8% labeled atropine from the uniformly labeled pentose. Expected yields of labeled furaldehydes, furoic acids, furans, and diethoxytetrahydrofurans can be calculated from the data presented and will vary, depending on which of the available pentoses is used and on whether one carbon of the uniformly labeled compound is lost during synthesis of the desired product.

Results of this investigation make available, for

the first time, a synthetic method for labeling the carbon skeleton of tropine, for synthesizing tropine-labeled atropine, and for synthesizing labeled intermediates between arabinose and tropine. Further studies will be published in the third paper of this series.

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Model Catalysts Which Simulate Penicillinase II

Mechanism of Hydrolysis of Penicillins Catalyzed by Catechol

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Studies have been made of the rates of loss of benzylpenicillin and methicillin from solutions containing catechol. The dependence upon pH of the specific rate constants for these hydrolyses catalyzed by monocatecholate ion is nonlinear, demonstrating the presence of metastable intermediates in the reaction pathway. The rates of penicillin loss at the higher pH's studied are faster than the rates of acid formation in the same systems indicating the presence of a covalent intermediate, probably catechol monopenicilloate. Analogy of this mechanism to that of hydrolyses of penicillins catalyzed by 3,6-bis(dimethylaminomethyl)catechol and by penicillinase is discussed.

IT WAS PREVIOUSLY reported that the compound 3,6-bis(dimethylaminomethyl)catechol (CDM) rapidly catalyzed the hydrolysis of penicillin to penicilloic acid (1). Pyrocatechol itself, as the monoanion, was also shown to be catalytic but at a much lower rate than CDM. Studies of the relationship between structure of the catalyst and its reactivity revealed that the catalytic efficiency of CDM was at least partly due to an ionic interaction between catalyst and substrate, similar to the type of interaction which might be expected in formation of an enzyme–substrate complex. It was speculated at that time that this reaction proceeded by covalent catalysis (2) to form a penicilloate ester of the catecholamine which would then be rapidly hydrolyzed to product, releasing free catalyst.

$$\text{penicillin} + \text{CDM} \rightarrow \text{ester} \rightarrow \text{penicilloic acid} + \text{CDM}$$

The above-mentioned studies were conducted by measuring the rate of acid production by means of a pH-stat. The presence of an ester intermediate might be demonstrated, however, by also following loss of penicillin. If the latter were more rapid than acid formation there would be no doubt as to the presence of an intermediate in the reaction pathway. The present report concerns the results of such studies in which pyrocatechol was utilized as the catalyst rather than CDM because it was felt that ester hydrolysis would be slower with pyrocatechol than with

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