[CONTRIBUTION FROM THE RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, AND DIVISION OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS AND COLLEGE OF PHARMACY, MEDICAL CENTER, UNIVERSITY OF CALIFORNIA]

SYNTHESIS OF ETHANOL-1-C^{14}, ETHANOL-2-C^{14}, ETHYL BROMIDE-1-C^{14}, ETHYL BROMIDE-2-C^{14} AND C^{14}-LABELED METHADONE[1]

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In order to know more exactly how the analgesic methadone (4,4-diphenyl-6-dimethylamino-3-heptanone) (1, 2) acts in the animal body, we have prepared this compound with C^{14} in the 2-position by the following series of reactions:

$$CH_3\overset{*}{C}O_2Na \xrightarrow{(C_2H_5)_2SO_4} CH_3\overset{*}{C}O_2C_2H_5 \xrightarrow[\text{Copper Chromite}]{H_2}$$

$$CH_3\overset{*}{C}H_2OH \xrightarrow{PBr_3} CH_3\overset{*}{C}H_2Br \xrightarrow{Mg} CH_3\overset{*}{C}H_2MgBr$$

$$\text{1. } (CH_3)_2NC(CH_3)(H)-CH_2C(C_6H_5)_2CN \xrightarrow[\text{2. HBr, } H_2O]{} (CH_3)_2NC(CH_3)(H)-CH_2C(C_6H_5)_2-C(=O)-\overset{*}{C}H_2CH_3\cdot HBr$$

In a similar manner, 4,4-diphenyl-6-dimethylamino-3-heptanone-1-C^{14} has been prepared using acetic acid-2-C^{14} as the starting material.[2] The carboxyl- and methyl-labeled acetic acids were prepared by previously published procedures (3, 4, 5, 6).

The methadone-2-C^{14} was prepared with a very high specific activity (0.5 μc/mg.), whereas the activity of the 1-labeled compound was only a few hundred counts/min/mg. In Table I the yields, specific activities, and scale of reactions are summarized for these two preparations. Animal studies on the *dl*-methadone-2-C^{14} are in progress in the Division of Pharmacology, and the results will be published elsewhere.

EXPERIMENTAL

Preparation of labeled ethyl acetate. Labeled sodium acetate (0.7–1.0 g.) was dried *in vacuo* to about 1 μ pressure and weighed into a 30-ml. acetylation flask fitted with a 14/20 standard joint. Five ml. of redistilled diethyl sulfate was added to the flask, and a low temperature (Dry Ice) reflux condenser attached (see Fig. 1). The reaction mixture was heated on an oil-bath at 150–170° for 1–1.5 hours. The unit was then connected to the

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[2] The nomenclature system for the labeled organic compounds is the same as that described in reference (4). For a similar scheme see Otvos and Wagner, *Science*, **106**, 409 (1947).

vacuum line (see Fig. 2) and the ethyl acetate distilled *in vacuo* from the diethyl sulfate. All but a trace of high-boiling impurities (mostly diethyl sulfate) were then removed by a second vacuum distillation. The yield of ethyl acetate by this method is 95–97% as deter-

TABLE I

PREPARATION OF METHADONE-2-C^{14}

	WEIGHT, GM.	M MOLE	SP. ACT. μC/MG	YIELD % BASED ON CO_2
$BaCO_3$	2.04	13.5	2.59	—
Sodium acetate-1-C^{14}	0.697	8.5	6.2	86[a]
Ethyl bromide-1-C^{14}	1.43	13.1	—	66.2
Methadone-2-C^{14}	1.00	2.56	0.55	9.5

[a] This yield was low; other radioactive runs have given yields of 91.3, 93.0, and 94.2%

PREPARATION OF METHADONE-1-C^{14}

	WEIGHT, GM.	M MOLE	SP. ACT. CTS/MIN/MG	YIELD % BASED ON CO_2
Sodium acetate-2-C^{14}	1.01	12.3	4.88×10^3	63.7
Ethyl bromide-2-C^{14}	2.05	18.8	—	46.0
Methadone-1-C^{14}	1.20[b]	3.22[b]	4.08×10^2	12.5

[b] Not all of the ethyl bromide was used in this condensation.

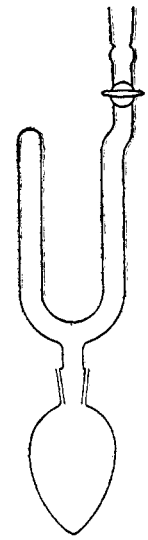

FIGURE 1

mined by saponification of the ester. A small amount of diethyl ether is present in the ethyl acetate.

Preparation of labeled ethanol. The ethyl acetate prepared as described was vacuum distilled into a 115 ml. hydrogenation bomb,[3] charged with 5 g. of copper chromite catalyst (7). When the distillation was completed, the bomb was closed, warmed to room

[3] American Instrument Company, Micro bomb, 180 ml. capacity.

temperature, filled with hydrogen to 2500 psi, and heated, with shaking, for 10 hours at 250°.

After the bomb had cooled to room temperature, it was reconnected to the vacuum line and the hydrogen removed by discharging the bomb contents through a liquid nitrogen-cooled spiral trap (see Fig. 2).

After the hydrogen was removed, the bomb was evacuated and the volatile contents of the bomb, as well as those in the warmed spiral trap, were vacuum distilled into the larger trap on the manifold. This product, a mixture of ethanol, water, and diethyl ether was treated without purification with phosphorus tribromide to prepare the halide.

To identify and isolate the ethanol, the mixture from a preliminary run was dried with calcium sulfate and distilled *in vacuo* into a micro distilling column pot. The ethanol was identified by its boiling point, 76–78°, and index of refraction, n_D^{17} 1.3624.

Preparation of ethyl bromide. The mixture of alcohol and water from the hydrogenation was distilled *in vacuo* into the bromination unit shown in Fig. 3. This unit was removed

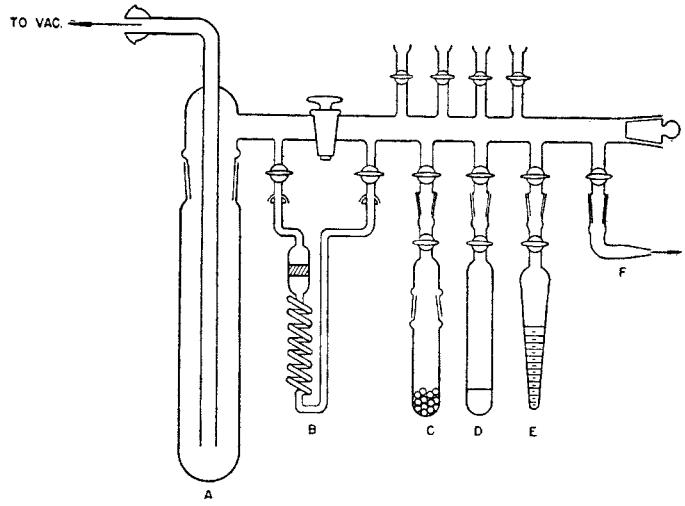

FIGURE 2

from the vacuum line and a second low-temperature condenser of the type shown in Fig. 1 connected to the ground joint. Both condensers were then cooled with Dry Ice-isopropyl alcohol, and phosphorus tribromide was added drop-wise to the alcohol-water mixture. A large excess of phosphorus tribromide (2–3 ml.) was added, and the mixture refluxed for 3 hours on a steam-bath. The entire bromination assembly was then connected to the vacuum line, and the ethyl bromide, together with some volatile impurities, distilled into the large trap on the manifold.

The product mixture was vacuum distilled into a reaction tube containing 10 ml. of 1 *N* sodium hydroxide solution (see Fig. 2-D). The vessel was removed from the line and shaken for several minutes to remove acid impurities. To dry the ethyl bromide it was then distilled *in vacuo* (together with some water) into a second reaction tube containing about 1 g. phosphorus pentoxide (Fig. 2-C). This mixture was also warmed to room temperature and shaken several minutes. The ethyl bromide was vacuum distilled into yet a third reaction vessel and shaken with 5 ml. of concentrated sulfuric acid for several minutes to remove ether and olefins. The purified ethyl bromide was distilled into a storage vessel (Fig. 2-E). The halide was identified on an inactive run by its boiling point, 34–39°, and its index of refraction, n_D^{18} 1.4326. The yield of ethyl bromide was 67–77% based on acetic acid.

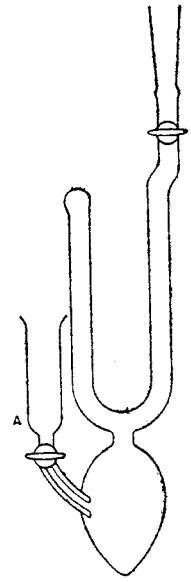

FIGURE 3

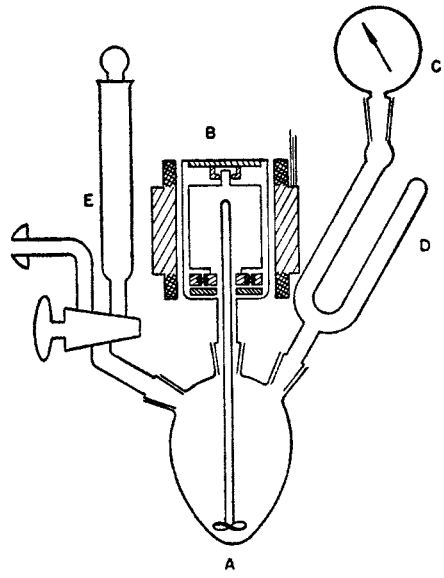

FIGURE 4

Purification of 2,2-diphenyl-4-dimethylaminopentanenitrile. The nitrile, donated by Eli Lilly and Company, was decolorized with Norit A and recrystallized three times from 80% ethanol. The product, consisting of large white prisms, was dried with calcium chloride *in vacuo*, m.p. 91–91.2°.

Anal. Calc'd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06.
Found: C, 81.98, 81.97; H, 7.95, 7.80; N, 10.26, 10.28.

Preparation of the labeled ethyl Grignard and condensation with the nitrile. The ethyl

Grignard was prepared on the vacuum line and the nitrile added in benzene solution. The apparatus for the reaction is shown in Fig. 4. Nitrogen was admitted to the dried, well-evacuated system containing 0.35 g. of magnesium turnings. Ten ml. of dry ether was then pipetted into the reaction flask through the stirrer opening. After the stirrer was replaced, the ether was frozen in liquid nitrogen and the system was re-evacuated. Labeled ethyl bromide (approximately 1 ml.) was vacuum distilled into the flask which was then closed from the manifold. With an ice-acetone mixture in the condenser the ether solution was refluxed, with stirring, for 1 hour. Through the dropping-funnel was then added 2.35 g. of the nitrile dissolved in 6 ml. of dry benzene. The dropping-funnel was washed twice with 1 ml. of dry benzene; the benzene solution was added slowly enough that no air was drawn into the reaction vessel. The solution was then refluxed for 3 hours; a white precipitate formed. The Grignard flask was transferred to the hood, cooled to 0°, opened, and 24.4 ml. of 20% hydrobromic acid solution added drop-wise to decompose the Grignard complex.

Purification of the methadone. The impure methadone solution was transferred to an Erlenmeyer flask and heated on the steam-bath. After the ether and benzene were boiled off, the acid solution was cooled and extracted with ether. The water layer was made alkaline with 20 ml. of 3 *N* sodium hydroxide and extracted with ether. The ether extract from the alkaline solution was evaporated to a small volume, and 2 ml. of 20% hydrobromic acid was added. The acid solution was heated on a steam-bath again to expel ether. Then a few ml. of absolute ethanol was added. The ethanol solution was concentrated on the steam-bath, and the *methadone hydrobromide* crystallized out, filtered, and recrystallized from 80% ethanol. The absorption spectra and analgesic properties of the active and inactive samples of methadone produced were checked with samples prepared by Eli Lilly and Company and found to be the same, m.p. 224°.

Anal. Calc'd for $C_{21}H_{28}BrNO$: C, 64.61; H, 7.23.
Found: C, 65.23, 65.22; H, 7.27, 7.40.

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SUMMARY

1. Semi-micro, high yield synthetic procedures have been developed for ethanol-1-C^{14}, ethanol-2-C^{14}, ethyl bromide-1-C^{14}, and ethyl bromide-2-C^{14}.

2. *dl*-Methadone (4,4-diphenyl-6-dimethylamino-3-heptanone) has been prepared labeled with C^{14} in either the 1 or 2 position.

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