SYNTHESIS OF PHENOBARBITAL -2-^{14}C.

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The previously reported synthesis of phenobarbital-2-^{14}C (1) and those of other barbituric acids labeled in the 2-position with carbon-14 (2,3), have employed the base catalysed condensation of the corresponding ester with urea. Although this reaction gives 60-80% yields of various 5,5 dialkyl substituted barbituric acids, attempts in our laboratories to obtain economically satisfactory amounts of phenobarbital-2-^{14}C using this reaction resulted in erratic yields varying from 6-20%. An analysis of the reaction mixture indicated that instead of condensing with urea the diethyl ethylphenylmalonate was undergoing decarboxylation to give sodium carbonate and ethyl α-phenylbutyrate. This side reaction in the preparation of various substituted barbituric acids was previously noted but was reportedly overcome by using an excess of urea, and avoiding a large excess of base. Since an excess of urea-^{14}C was not practical, an old synthesis first reported by Fischer and Dilthey (5) for 5,5-dialkyl barbituric acids and later reported as a method for phenobarbital (6) was investigated. This synthesis involved heating the ethyl-

phenylmalonly chloride with urea at 100°. This reaction was experimentally easier to carry out and gave easily reproducible yields in the range 40-50% with an average value of about 47%. Using this method 35.6 mc of phenobarbital-2-^{14}C were prepared from 74.4 mc of urea, 48% yield. The product crystallized in polymorphic from V but was converted into polymorphic form I or II on recrystallization from water (7).

Phenobarbital-2-^{14}C. To 3.80 g of ethylphenylmalonyl chloride (8) stirring in a 100° oil bath was added in portions 900 mg. of urea-^{14}C (74.4 mc). To prevent loss of radioactive material into the atmosphere, two Dry Ice-isopropanol traps and a 40% KOH trap were used. The urea dissolves with evolution of a gas. After about two hours the mixture solidifies. Vacuum, ca. 80 mm., is applied and heating is continued for 18 hours. The oil bath was removed and the solid, 3.40 g., was extracted with petroleum ether. The remaining solid, 3.10 g., was extracted with ether. The resulting ether insoluble oil was dissolved in ethyl acetate and some additional labeled product was recovered by two additions of 400 mg. each of nonlabeled product followed by removal of the ethyl acetate, *in vacuo* and extraction of the residue with ether. The three ether extracts were combined and after removal of the solvent *in vacuo*, the residue was crystallized and recrystallized from water until the specific activity was constant to give 2.063 g. of phenobarbital-^{14}C, m.p. 174-175°, 361 μc/mM. The mother liquors were combined and concen-

trated to dryness in vacuo. The product present was partially separated from some oily material by filtration of an ether solution through a column prepared from 25 g. of silica gel. The fractions containing product were combined and after addition of 0.630 g. of nonlabeled phenobarbital the solvent was removed in vacuo. The residue was crystallized and recrystallized from water until the specific activity was constant, to give 0.777 g. of phenobarbital-2-^{14}C, m.p. 173.5-174.5°, 105 μc/mM. Total yield based on radioactivity is 48%.

The chemical identity of the product was shown by a comparison of its infrared spectrum with that of an authentic sample in 0.75% chloroform solution and in potassium bromide pellets. The product was shown to be radiochemically pure by radio-thin-layer-chromatography on Silica Gel G plates in two solvent systems: ether and chloroform-methanol (9:1).

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