# Radiosynthesis of Carbon-14–Labeled 4-Dimethylamino-3,5-xylyl Methylcarbamate

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4-Dimethylamino-3,5-xylyl methylcarbamate was labeled with carbon-14 at three locations. The carbonyl group was labeled in 46% yield based on radioactivity by the conversion of acetic anhydride-1,1-$C^{14}$ to methyl isocyanate and reaction of this with 4-dimethylamino-3,5-xylenol. The 1-position in the ring was labeled in 3% yield by the addition of carbon dioxide-$C^{14}$ to the di-Grignard reagent of 1,5-dibromo-2,4-dimethylpentane and catalytic conversion to 3,5-xylenol. This was followed by nitrosation, hydrogenation, methylation, and reaction with methyl isocyanate. The di-Grignard reagent was prepared by a seven-step synthesis starting with diethyl malonate. Both the 3-position in the ring and the 3-methyl group were labeled in 10% yield by the reaction of acetaldehyde-1,2-$C^{14}$ with ethylacetoacetate and conversion to 3,5-xylenol.

ZECTRAN (registered trade-mark of The Dow Chemical Co.), 4-dimethylamino-3,5-xylyl methylcarbamate is a highly active material for control of mollusks and a large number of arthropod pests of plants (*14*). Its potential use on food crops necessitated a study of its metabolism in both plants and animals. Therefore, the radioactive synthesis of this compound labeled with $C^{14}$ in both the ring and the carbamate functional group was undertaken.

This paper describes the preparation of 4-dimethylamino-3,5-xylyl methylcarbamate - carbonyl - $C^{14}$; 4 - dimethylamino-3,5-xylyl-1-$C^{14}$ methylcarbamate; and 4 - dimethylamino - 3,5 - xylyl-$\alpha^3$, 3-$C^{14}_2$ methylcarbamate.

## Discussion

The reactions for the preparation of 4-dimethylamino-3,5-xylyl methylcarbamate - carbonyl - $C^{14}$ are shown in Figure 1.

Attempts to prepare methyl-$C^{14}$ isocyanate from silver isocyanate and methyl iodide or from methylamine hydrochloride and phosgene (*11*) were unsuccessful. An adaptation of the preparation of methyl isocyanate reported by Colucci (*1*) was used. Heating for $7^1/_2$ hours gave a maximal yield (46%). Work by Krishna, Dorough, and Casida (*7*) and Metcalf, Fukuto, and Winton (*8*) showed the preparation of radioactive carbamates using a similar procedure.

The reactions for the preparation of 4 - dimethylamino - 3,5 - xylyl - 1 - $C^{14}$ methylcarbamate are shown in Figures 2 and 3.

Since phenol has been prepared by reaction of cyclohexanone with nickel or copper catalyst at 280° C. (*13*) and cyclohexanone has been prepared by adding carbon dioxide to the di-Grignard reagent of 1,5-dibromopentane (*4*), the logical approach was to synthesize 1,5-dibromo-2,4-dimethylpentane. An attempt to prepare 2,4-dimethyl-1,5-pentanediol from the di-Grignard reagent of 1,5-dibromopentane and paraformaldehyde failed. An unsuccessful effort was made to prepare diethyl 2,4-dimethylglutarate from dimethyl glutarate, methyl iodide, and sodium hydride; under these conditions, the ester underwent self-condensation and no alkylation occurred.

The reactions for the preparation of 4 - dimethylamino - 3,5 - xylyl - $\alpha^3$, 3-$C^{14}_2$ methylcarbamate are shown in Figure 4.

Early experimental work has shown that 3,5-dimethylcyclohexanone could be converted into 3,5-xylenol in a 25% yield by aromatization over a nickel catalyst. Further investigation showed that the same type of reaction applied to 3,5 - dimethyl - 2 - cyclohexen - 1 - one resulted in a 50% yield of 3,5-xylenol. Inasmuch as 3,5-dimethyl-2-cyclohexen-1-one could be prepared from acetaldehyde and the synthesis of doubly labeled acetaldehyde had been described in considerable detail, it was decided to use this compound as an intermediate in the synthesis of labeled Zectran. The 3,5-xylenol resulting was labeled both in the 3-position of the ring and in the 3-methyl group.

## Experimental

**4-Dimethylamino-3,5-xylyl Methylcarbamate-carbonyl-$C^{14}$.** METHYL ISOCYANATE-$C^{14}$. Sodium azide (78.8 mg., 1.2 mmoles), prepared according to the procedure of Smith (*12*), 1.06 mmoles of acetic anhydride-1,1-$C^{14}_2$, and 1 ml. of anhydrous benzene were heated with shaking at 100° C. in a sealed tube for $7^1/_2$ hours (*1*). This preparation was used directly in the next synthesis.

4 - DIMETHYLAMINO - 3,5 - XYLYL METHYLCARBAMATE-CARBONYL-$C^{14}$. The tube containing the methyl isocyanate-$C^{14}$ was opened and 165 mg. (1 mmole) of 4-dimethylamino-3,5-xylenol and 1% triethylamine in 1 ml. of anhydrous benzene were added. The tube was resealed and allowed to stand at room temperature for $18^1/_2$ hours. The tube was opened and 1.5*N* NaOH was added. The alkaline layer was removed, and the benzene was washed with two 1-ml. portions of water. The benzene was evaporated, and the residue was dried in vacuo.

The crude product was dissolved in a minimum of carbon disulfide and passed through a column (8.5 × $^3/_8$ inch) containing Alcoa F-20 alumina that had been equilibrated with 10% water 24 hours before use, using carbon disulfide as the developing solvent. The eluate from 40 to 70 ml. contained product—79 mg. (35% yield based on radioactivity). The melting point, 81–83° C., was identical to that of an authentic sample of Zectran.

**4-Dimethylamino-3,5-xylyl-1-$C^{14}$ Methylcarbamate.** DIETHYL 2,4-DICARBETHOXYGLUTARATE (*5*). To a solution of 18.4 grams (0.8 mole) of sodium in 400

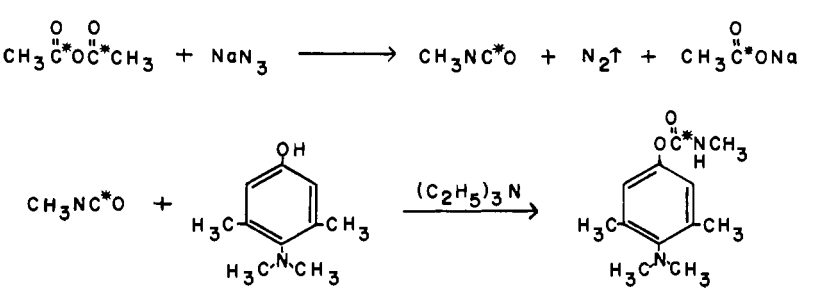


Figure 1. Synthesis of 4-dimethylamino-3,5-xylyl methylcarbamate-carbonyl-$C^{14}$

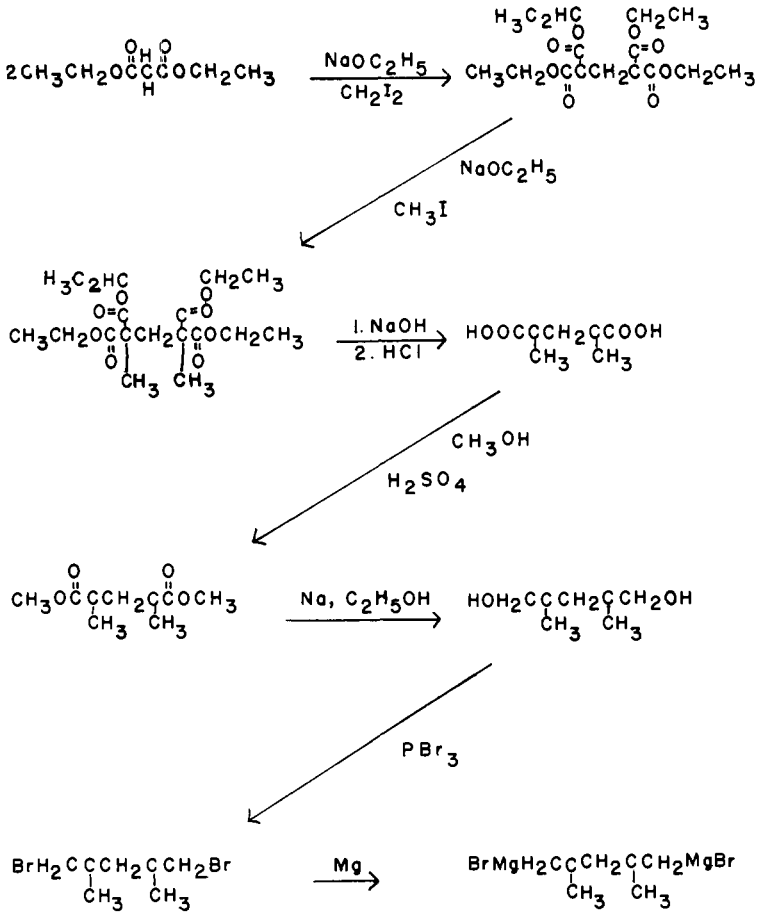

Figure 2. Synthesis of 4-dimethylamino-3,5-xylyl-1-$C^{14}$ methylcarbamate

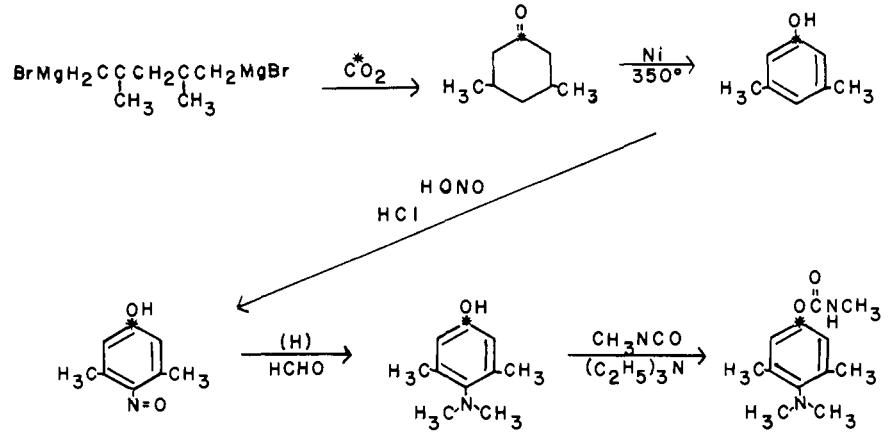

Figure 3. Synthesis of 4-dimethylamino-3,5-xylyl-1-$C^{14}$ methylcarbamate

ml. of anhydrous ethanol were added 128 grams (0.8 mole) of diethyl malonate and 108 grams (0.4 mole) of diiodomethane. The reaction was refluxed for 2 hours, cooled to room temperature, and poured into a mixture of 400 grams of crushed ice, 400 ml. of water, and 60 grams of potassium dihydrogen phosphate. The aqueous solution was extracted seven times with 200-ml. portions of ether. The ether extracts were combined and dried over magnesium sulfate, and the ether was removed by distillation through a 10-inch Vigreux column. The residue was distilled in vacuo to give 106 grams of a colorless liquid which solidified upon standing (40% yield, b.p. = 120° C. at 0.4 mm.).

2,4-Dimethylglutaric Acid (*3*). To a solution of 14.7 grams (0.64 mole) of sodium in 375 ml. of anhydrous ethanol were added 106 grams (0.32 mole) of diethyl 2,4-dicarbethoxyglutarate followed immediately by the addition of 102.5 grams (0.72 mole) of methyl iodide. The mixture was refluxed for $2^1/_2$ hours and cooled to room temperature. To the mixture were added 360 ml. of 6*N* NaOH, and refluxing was continued for 19 hours. Then 180 ml. of concentrated HCl were added, and the sodium chloride was filtered off. The ethanol was removed in vacuo, 400 ml. of concentrated HCl were added to the residue, and the solution was refluxed for 18 hours. It was then concentrated to 200 ml. in vacuo, and a solution of sodium bisulfite was added. The acidic solution was extracted six times with 200-ml. portions of ether. The ether extracts were combined and dried over magnesium sulfate, and the ether was removed in vacuo, leaving 50 grams of residue.

Dimethyl 2,4-Dimethylglutarate. Fifty grams (0.36 mole) of 2,4-dimethylglutaric acid, 250 ml. of methanol, and 10 ml. of concentrated $H_2SO_4$ were refluxed for 17 hours. The methanol was removed in vacuo, and the residue was taken up in ether. The ether was shaken with 110 ml. of 20% sodium carbonate and separated, and the carbonate solution was extracted two times with ether. The ether layers were combined, washed three times with sodium bisulfite, once with water, and dried over magnesium sulfate, and the ether was removed by distillation. The residue was distilled in vacuo to give 37 grams (62% yield, b.p. = 79–88° C. at 1.9 mm., $n_D^{22}$ = 1.4252).

2,4-Dimethylpentane-1,5-diol.. To 37 grams (0.2 mole) of dimethyl 2,4-dimethylglutarate in 300 ml. of anhydrous ethanol were added 37 grams (1.6 moles) of sodium in small pieces. After the sodium had dissolved, the solution was diluted with water, and the ethanol was removed in vacuo. The aqueous solution was saturated with potassium carbonate and continuously extracted with ether for 16 hours. The ether was dried over magnesium sulfate and distilled off, and the residue was distilled in vacuo to give 11 grams of colorless liquid [42% yield, $n_D^{20}$ = 1.4553; lit. (*10*) $n_D^{20}$ = 1.4549].

1,5 - Dibromo - 2,4 - dimethylpentane. This compound was prepared from 11 grams (0.083 mole) of 2,4-dimethylpentane-1,5-diol and 15.3 grams (0.0565 mole) of phosphorus tribromide, according to the procedure of Noller and Pannell (*10*). Distillation at reduced pressure gave 7.6 grams of colorless liquid (37% yield, $n_D^{20}$ = 1.5050; lit. $n_D^{20}$ = 1.5042).

Di-Grignard Reagent of 1,5-Dibromo-2,4-dimethylpentane. The di-Grignard reagent was prepared from 0.53 gram (22 mmoles) of magnesium (ground in a Wiley mill) and 2.58 grams (10 mmoles) of 1,5-dibromo-2,4-dimethylpentane in 6 ml. of ether. After $6^1/_2$ hours' refluxing, titration with hydrochloric acid showed 5.2 mmoles (52% yield) of the di-Grignard reagent.

3,5-Dimethylcyclohexanone - 1 - $C^{14}$. Two millimoles of carbon-$C^{14}$ dioxide were prepared from 394.8 mg. of barium carbonate-$C^{14}$ and 6 ml. of concentrated $H_2SO_4$ in the vacuum manifold. The carbon-$C^{14}$ dioxide was allowed to react with 2 mmoles of the di-Grignard reagent of 1,5-dibromo-2,4-dimethylpentane and 25 mg. of cuprous chloride catalyst in ether. The mixture was stirred and heated at 40° to 50° C. at 1.5-atm. pressure. After 10 minutes, the ether was removed in vacuo and the residue was acidified with 6*N* HCl

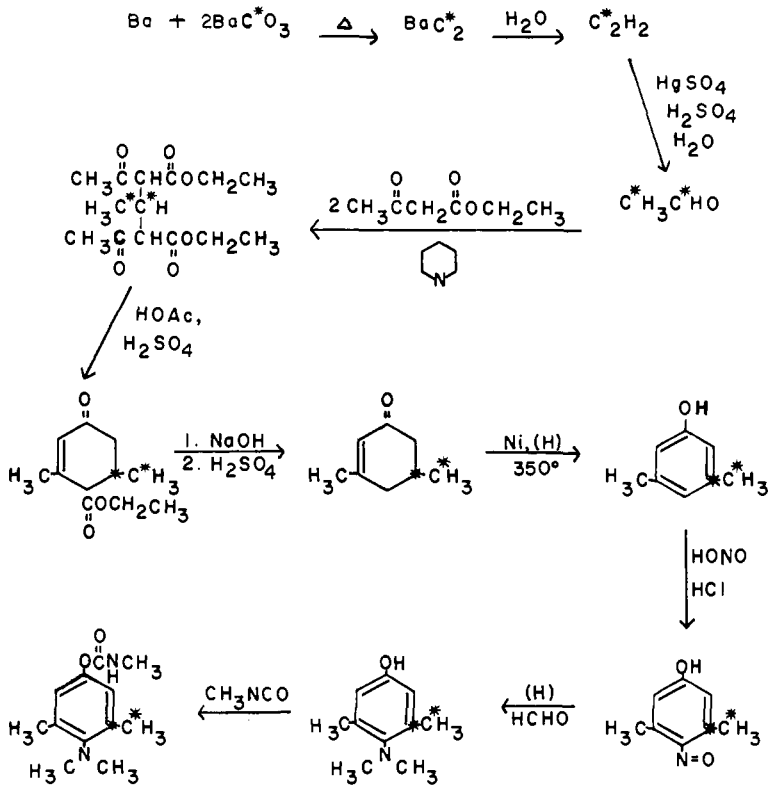

Figure 4. Synthesis of 4-dimethylamino-3,5-xylyl-$\alpha^3$,3-$C^{14}_2$ methylcarbamate

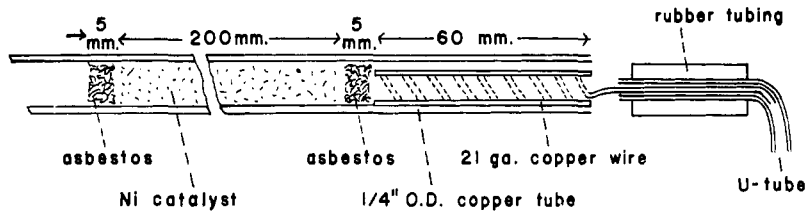


Figure 5. Detail of aromatization catalyst packing in combustion tube

and steam-distilled. Four 8-ml. fractions were collected, and each was extracted four times with ether. The extracts were combined and dried over magnesium sulfate, and the ether was removed, using a bath temperature of 60° C., through a tube (1 meter × 8 mm.). The residue was passed through a 5-foot-long vapor-phase chromatography column packed with Craig ester (butanediol succinate on acid-washed Chromosorb, obtained from Wilkens Instrument Co.) at 145° C., and the fraction corresponding to known 3,5-dimethylcyclohexanone was collected in a U-tube (8-mm. o.d. and drawn to a tubulation to fit the end of the reaction tube) immersed in a dry ice bath. The product weighed 50 mg.

3,5-Xylenol-1-$C^{14}$. Preparation of Aromatization Catalyst. The aromatization catalyst was prepared by stirring 50 grams of Dicalite into a solution of 17.6 grams of nickelous sulfate hexahydrate in 250 ml. of water. Twenty-two milliliters of 6*N* NaOH were added dropwise, with stirring, to the slurry. Stirring was continued for 10 minutes, and the solid was filtered off and washed with water until the filtrate was free of sulfate.

Packing the Catalyst Tube. A 11.25- × 525-mm. silica combustion tube with side arm was provided with a $^1/_8$-inch-diameter spiral of No. 21 copper wire at one end. The copper spiral was placed concentric to a 6-cm. length of $^1/_4$-inch copper tubing (outside diameter) behind which was placed a loosely packed $^1/_2$-cm. band of long-fiber asbestos. This was followed by a 20-cm. band of the nickel oxide–Dicalite catalyst, a $^1/_2$-cm. band of asbestos, another 20 cm. of catalyst, and a final $^1/_2$-cm. band of asbestos. (The details of this packing are shown in Figure 5.)

Activation of Catalyst. The combustion tube was placed in a suitable tube furnace, and the temperature was raised to 600° C. as a slow stream of hydrogen was passed through the tube. When the catalyst had become uniformly black in color, the hydrogen was replaced by a nitrogen stream; and the tube was permitted to cool to room temperature as the nitrogen flowed through it.

Aromatization of 3,5-Dimethylcyclohexanone-1-$C^{14}$. The catalyst contained in the combustion tube was placed in a suitable tube furnace and heated to 320° C. The wide mouth of the combustion tube was closed with a rubber stopper. The side arm was attached to the U-tube in which the cyclohexanone had been collected. A similar tube, surrounded by crushed dry ice, was used as a collection vessel. Nitrogen was passed through at a rate of 5 ml. per minute. The time required for the aromatization reaction was about 48 hours.

The U-tube was rinsed with two successive 1-ml. portions of peroxide-free ether. The combined ether extracts were washed with 1 ml. of 2*N* NaOH and then 1 ml. of water. The aqueous phases were combined, acidified with 0.2 ml. of concentrated HCl, and extracted with five 0.4-ml. portions of peroxide-free ether. The combined ether extracts were dried over magnesium sulfate and concentrated through a tube (1 meter × 8 mm.) at 60° C. The last trace of solvent was removed under vacuum to give 17.6 mg. (36% yield) of viscous, colorless oil.

4-Nitroso-3,5-xylenol-1-$C^{14}$. A solution of 60 mg. (0.868 mmole) of sodium nitrite in 0.2 ml. of water was added dropwise to 17.6 mg. of 3,5-xylenol-1-$C^{14}$ and 20.6 mg. of inactive 3,5-xylenol (0.313 mmole total) in 0.35 ml. of ethanol and 0.3 ml. of concentrated HCl. The mixture was stirred for 20 minutes. The resulting precipitate was filtered with suction, washed with water, and dried in vacuo over calcium chloride for 3 hours.

4-Dimethylamino-3,5-xylenol-1-$C^{14}$. The 4-nitroso-3,5-xylenol-1-$C^{14}$ and 10 mg. of sodium acetate trihydrate in 2.5 ml. of methanol were added to an equilibrated mixture of 100 mg. of 5% palladium on charcoal (Matheson Coleman & Bell) and 4 ml. of methanol in an atmosphere of hydrogen. After the reaction was complete, 0.183 ml. of 37% formalin in 1 ml. of methanol was added. Hydrogen uptake showed 30.9 mg. of product. The mixture was filtered, the charcoal was washed with methanol, and the methanol was removed from the filtrate in vacuo. Ice was added, and the mixture was extracted twice with methylene chloride. The extracts were combined and the solvent was removed, using a 65° C. water bath through a tube (42 × 0.5 cm.). The solid residue was purified by sublimation in vacuo at 10-micron pressure, using a 150° C. bath. The path length was 0.6 cm. (Scientific Glass JM-7335).

4-Dimethylamino-3,5-xylyl-1-$C^{14}$ Methylcarbamate. The 4-dimethylamino-3,5-xylenol-1-$C^{14}$, 100 μl. of freshly distilled methyl isocyanate, and 1 ml. of hexane containing 1% triethylamine were allowed to stand for 24 hours in a stoppered flask. The hexane was evaporated using a 65° C. water bath, and the last traces were removed in vacuo. The residue was dissolved in 1 ml. of carbon disulfide and passed through an alumina (10% water) column (8.5 × $^3/_8$ inch) with carbon disulfide as the developing solvent. Forty through 90 ml. of effluent were evaporated at reduced pressure to give

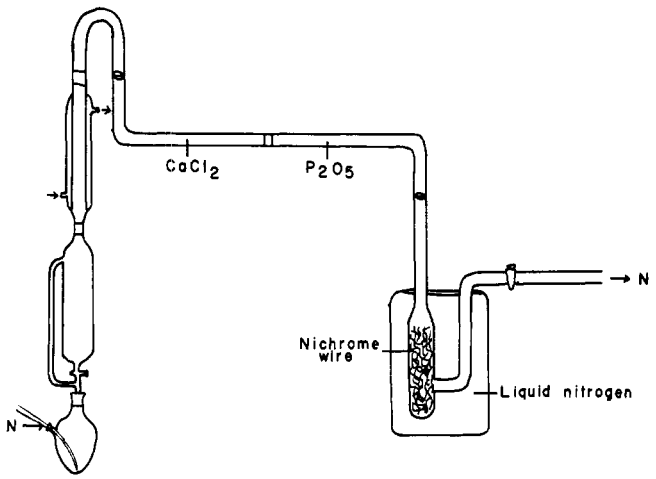


Figure 6. Apparatus used in preparation of acetylene

12.9 mg. (3% yield based on radioactivity) of colorless, crystalline product.

**4 - Dimethylamino-3,5 - xylyl - $\alpha^3$,3-$C^{14}_2$ Methylcarbamate.** ACETYLENE-1,2-$C^{14}_2$. A modification of the procedure of Monat, Robbins, and Ronzio (*9*) was used. Two millimoles of barium carbonate-$C^{14}$ were fused with excess barium metal shavings in an atmosphere of argon. A 6-inch borosilicate glass test tube was drawn into a cone at the bottom, inclined at a 45° angle, and heated with a Bunsen burner. The barium carbonate was deposited on top of the barium and then covered with more barium. After the fusion was complete, the tube was broken above the fused mass and transferred to a 20-ml. pear-shaped flask with side arm. Twelve milliliters of water were dropped onto the barium carbide-$C^{14}$, and the resultant acetylene-1,2-$C^{14}_2$ was passed through a condenser, calcium chloride, and phosphorus pentoxide, and collected in a trap containing Nichrome wire at −194° C. (The apparatus is shown in Figure 6.) The water solution was boiled for 10 minutes, then nitrogen was passed through the apparatus at a rate of 7.7 ml. per minute for 15 minutes.

ACETALDEHYDE-1,2-$C^{14}_2$. A modification of the procedure of Cramer and Kistiakowsky (*2*) was used. The acetylene-1,2-$C^{14}_2$ was transferred on the vacuum manifold into a tube (10 inch × 2 cm.) containing 10 ml. of hydration catalyst (0.2 gram of $HgSO_4$ and 0.6 gram of concentrated $H_2SO_4$ in water) frozen in a shell, first in dry ice, then at −194° C. The tube was sealed under vacuum and heated in a boiling water bath for 5 minutes. The contents were frozen in a shell and immersed in liquid nitrogen. The tube was opened, and the contents were transferred into a 20-ml. pear-shaped flask with side arm. The mixture was distilled for 30 minutes while nitrogen was bubbled through at a rate of 1.3 ml. per minute (same apparatus as shown in Figure 6 without the calcium chloride and phosphorus pentoxide drying tubes). The acetaldehyde-1,2-$C^{14}_2$ was collected in a trap containing Nichrome wire protected from the atmosphere by a calcium chloride drying tube and immersed in liquid nitrogen.

3,5 - DIMETHYL - 5 - $C^{14}$ - 2 - CYCLOHEXEN-1-ONE-5-$C^{14}$ (*6*). The trap, still in liquid nitrogen, was transferred to the vacuum manifold and evacuated. A tube (8 × 1/2 inch) containing 0.3 ml. of ethyl acetoacetate was immersed in liquid nitrogen and evacuated on the vacuum manifold. The liquid nitrogen around the trap containing the acetaldehyde was replaced with a dry ice and acetone bath, and the acetaldehyde was transferred into the tube containing the ethyl acetoacetate. The tube was protected from moisture and warmed to 0° C. Ten microliters of a solution of 2 ml. of piperidine and 5 ml. of absolute ethanol were added, and the tube was stoppered and allowed to stand at 0° C. for 24 hours. Another 10 μl. of the piperidine-ethanol solution were added, and the reaction was allowed to stand at 0° C. for 24 hours. This was repeated once more.

One-fourth milliliter of glacial acetic acid and 2 drops of concentrated $H_2SO_4$ were added, and the mixture was heated on the steam bath for 1 hour. One gram of ice was added, and the mixture was extracted three times with 2 ml. portions of peroxide free ether. Ether extracts were combined with 2 ml. of water, and solid sodium carbonate was added until effervescence ceased. The ether was drawn off, and the aqueous phase was extracted three times with 2-ml. portions of peroxide-free ether. The ether extracts were combined and concentrated, using a 65° C. water bath, through a tube (42 × 0.5 cm.).

One-half milliliter of 2*N* NaOH and 2 drops of ethanol were added. A condenser was attached, and the mixture was heated on the steam bath until the ester dissolved and then was refluxed for 15 minutes with a free flame. The mixture was cooled and extracted three times with 3-ml. portions of peroxide-free ether. The ether extracts were combined, dried over magnesium sulfate, and concentrated, using a 65° C. water bath through a tube (42 × 0.5 cm.).

The residue was passed in 100-μl. portions through a vapor-phase chromatography column (5 feet × 1/2 inch) packed with butanediol succinate on acid-washed Chromosorb at 166° C., and the fraction corresponding to known 3,5-dimethyl-2-cyclohexen-1-one was collected. This gave 28 mg. (23% yield).

3,5-XYLENOL-$\alpha^3$,3-$C^{14}_2$. The aromatization catalyst was prepared, the catalyst tube packed, the catalyst activated, and the 3,5-dimethyl-5-$C^{14}$-2-cyclohexen-1-one-5-$C^{14}$ aromatized in the manner described for 3,5-dimethylcyclohexanone. The collecting U-tube was disconnected from the furnace and rinsed with three successive 1-ml. portions of peroxide-free ether. The extracts were combined, dried over magnesium sulfate, and concentrated through a tube (1 meter × 8 mm.) at 65° C. to give 16 mg. of product.

4 - DIMETHYLAMINO - 3,5 - XYLYL - $\alpha^3$,3-$C^{14}_2$ METHYLCARBAMATE. The 3,5-xylenol-$\alpha^3$,3-$C^{14}_2$ was diluted with 48 mg. of inactive 3,5-xylenol. The nitrosation, hydrogenation, and methylation were carried out as previously described. Reaction with methyl isocyanate gave a crystalline product. The yield was 103 mg., approximately 10% based on radioactivity; radioactive purity was 98%.

To test for radioactive purity, the product was developed on Whatman No. 1 paper as a descending paper chromatogram at room temperature with isoamyl alcohol–formic acid–water (12:1:7 v./v.) as the developing solvent.

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