

SYNTHESIS OF 3 OR 5 [ $^{14}\text{C}$ ] 4-BUTYL-1,2-DIPHENYL-3,5-PYRAZOLIDINEDIONE  
(PHENYLBUTAZONE).

S. Stavchansky and H.B. Kostenbauder.

College of Pharmacy,  
University of Kentucky  
Lexington, Kentucky 40506.

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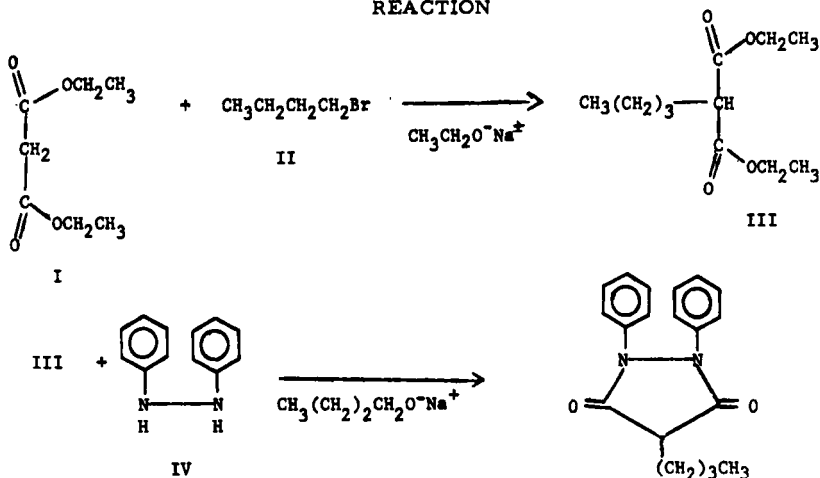
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SUMMARY

The condensation of 1 or 3 [ $^{14}\text{C}$ ] *n*-butylmalonate diethyl ester (III) with hydrazobenzene (IV) yields up to 90 per cent of 3 or 5 [ $^{14}\text{C}$ ] 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione, if *n*-butyl alcohol is used as a solvent and the corresponding sodium alcoholate as a condensing agent (1,2).

One or three [ $^{14}\text{C}$ ] *n*-butylmalonate diethyl ester can be synthesized by condensation of *n*-bromobutane (II) and 1 [ $^{14}\text{C}$ ] ethyl malonate (I) in the presence of sodium ethoxide (3).

REACTION



## PROCEDURE

A three neck 100 ml. flask, fitted with a rubber septum, a reflux condenser, and a thermometer, is clamped over a steam or a water bath. In the flask is placed 15 ml. of absolute ethanol<sup>a</sup> and then there is added gradually, through the condenser, 0.7 g. of clean sodium, cut into pieces of suitable size. If the reaction becomes very violent, the mixture may be cooled by pouring water over the outside of the flask. The sodium alcoholate solution is stirred and cooled to about 50° C, after which 5 g. (4.8 ml., 1 mc.) of diethyl malonate<sup>b</sup> is slowly added through a syringe. The temperature is raised to about 65° to 70° C, and to the clear solution is added gradually 3.97 g. (3.16 ml.) of *n*-butyl bromide<sup>c</sup>. The reaction commences almost immediately and considerable heat is generated. If the addition is too rapid the reaction may become violent enough to require cooling of the flask by pouring water over it.

The reaction mixture is refluxed until neutral to moist litmus, requiring about two hours. The flask is then connected with a condenser set for distillation. As much alcohol as possible is distilled off by means of the steam or water bath.

The residue from which no more alcohol can be distilled is treated with about 15 ml. of water and thoroughly shaken. The upper layer of *n*-butylmalonic ester is separated<sup>d</sup> and distilled under diminished pressure. First a low boiling portion is collected, consisting of alcohol, water and butyl bromide; then a small intermediate fraction of unchanged malonic ester comes over; and finally 1 or 3

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<sup>a</sup> The quality of the absolute ethanol has a very marked effect upon the yield.

<sup>b</sup> The malonic ester was obtained from New England Nuclear Corporation. The ester should be redistilled under diminished pressure and a 2 degree fraction used in the preparation.

<sup>c</sup> The *n*-butyl bromide should be redistilled.

<sup>d</sup> It is not practical to filter off the sodium bromide either before or after the distillation of the alcohol, as the separation of the ester from the water layer becomes very difficult.

[<sup>14</sup>C] *n*-butylmalonic ester boiling at 130°-135°C/20 mm., 140°-145°C/40 mm. or 235°-240°C/760 mm. The first fractions amount to ca. 0.5 ml., while the main fraction amounts to 80-90 per cent of the theoretical amount. Radioactive yield 84.7%, specific activity  $1.3 \times 10^{-1} \mu\text{c}/\text{mg}$ .

The structure of III was confirmed by infra-red and nuclear magnetic resonance spectroscopy.

1 OR 3 [<sup>14</sup>C] N-BUTYLMALONATE DIETHYL ESTER TO 3 OR 5  
[<sup>14</sup>C] 4-BUTYL-1,2-DIPHENYL-3,5-PYRAZOLIDINEDIONE

Into a three neck 150 ml. flask, fitted with a rubber septum, a condenser, a thermometer and a magnetic stirrer, is placed 29.7 ml. (24.0 g.) of butyl alcohol<sup>e</sup>. There is then added gradually, through the condenser, 0.4 g. of sodium, cut into pieces of suitable size. If the reaction becomes violent the mixture is cooled by pouring water over the outside of the flask. The sodium alcoholate solution is stirred and cooled to about 50°C, after which (3.0 g.) of hydrazobenzene<sup>f</sup> is added and dissolved in the reaction mixture. A small stream of nitrogen is passed into the flask, through the rubber septum. The temperature is raised to about 70°C, and to the clear orange solution, is added gradually through a syringe, 2.98 g. of 1 or 3 [<sup>14</sup>C] *n*-butylmalonate diethyl ester (387.4  $\mu\text{c}$ ).

The reaction mixture is refluxed for 18 hours. The flask is then connected with a condenser set for distillation. As much butyl alcohol as possible is distilled off by means of a heating mantle.

The residue from which no more alcohol can be distilled is cooled to about 50°C and treated with about 30 ml. of water and shaken thoroughly. The aqueous solution is then transferred to a separatory funnel and 100 ml. of ether is added

<sup>e</sup> The quality of the butyl alcohol has a very marked effect upon the yield. It is convenient to redistill it.

<sup>f</sup> It is indeed imperative to purify the hydrazobenzene.

to dissolve the unreacted hydrazobenzene. The aqueous solution is then acidified with hydrochloric acid. A white precipitate is formed consisting of 3 or 5 [ $^{14}\text{C}$ ] 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione.

The precipitate is filtered through a Buchner funnel and recrystallized in ethanol-water. Crystals from ethanol, mp.  $105^{\circ}\text{C}$ , yield 90%, specific activity  $8.3 \times 10^{-2}$   $\mu\text{c}/\text{mg.}$ , radioactive yield 93.0%. Radioactive purity of the final product was determined by thin layer chromatography using Silica Gel G and 2-butanone as the mobile phase (4). Only one spot was observed after exposure to iodine vapor. Radioactive scanning of the plate shows over 98% purity.

Structure determination was confirmed by nmr and infra-red spectroscopy.

All radioactivity measurements were made using a Packard Tri Carb Scintillation Spectrometer, Model 3375, with efficiency of 90% and background count of 30 cpm. The samples were counted in a liquid scintillation cocktail containing 4 g. of 2,5-diphenyloxazole (PPO), 100 mg. of 1,4-bis[2-(4-methyl-5-phenyloxazolyl)]-benzene, and 370 g. of Triton X-100 made up to a liter with distilled toluene<sup>g</sup>.

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<sup>g</sup> All the cocktail chemicals were purchased from Packard Company, Downer's Grove, Illinois, U. S. A.

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