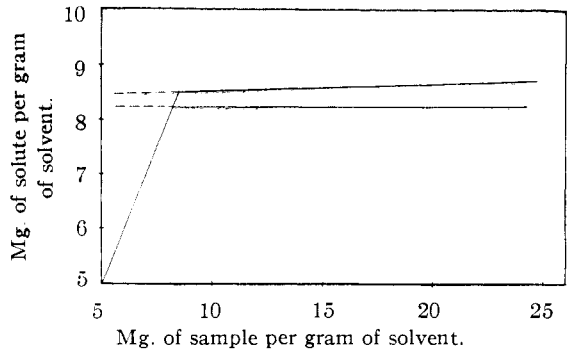


Fig. 1.—Solubility analysis of samples B (sloped line) and C (horizontal line).

and γ-isomers and that the reaction products of the azide with penicillamine and of III with penicillamine methyl ester may be mixtures of α- and γ-glutamyl derivatives instead of the substance constituting the title of their paper.

Experimental

N-Phenylacetyl-L-glutamic acid was prepared and dehydrated exactly as described.[1] The anhydro derivative was ammonolyzed exactly as described and the crude product melted at 131–136° (A). Several recrystallization of this material from acetone–petroleum ether (b.p. 60–80°) gave a product melting at 144–146° (B), as described. Pure material, m.p. 148–149° (C) was obtained as the insoluble residue in the equilibrated ampoules of (B) which were used in the solubility analysis.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.09; H, 6.06; N, 10.60. Found: Sample A: C, 60.33; H, 6.83; N, 10.12. Sample B: C, 58.75; H, 6.33; N, 10.88. Sample C: C, 59.09; H, 6.36; N, 10.54.

A mixture of 1.06 g. (4 millimoles) of sample, 4 cc. of pyridine and 4 cc. of acetic anhydride was refluxed until gas evolution ceased, the envolved gas being collected over water saturated with carbon dioxide. The volumes of carbon dioxide evolved, corrected for the blank on the apparatus, probably accurate within ±5 cc. were: sample A, 28 cc.; sample B, 9 cc.; sample C, none.

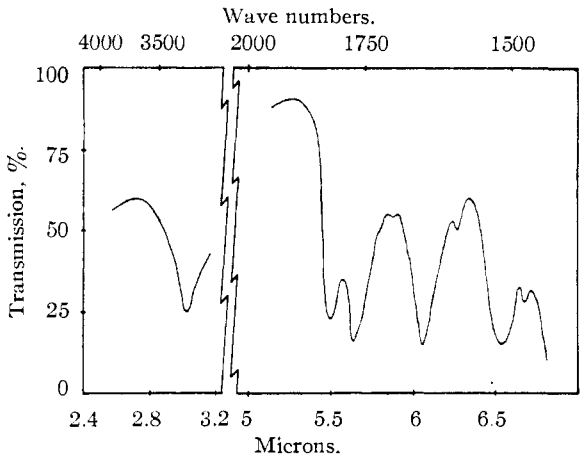


Fig. 2.—Infrared spectrum of anhydrophenacetylglutamic acid.

Solubility analyses were done in purified acetone, using about 8 g. of solvent in sealed glass ampoules which were constantly tumbled in a thermostatically controlled water-bath at 25.0 ± 0.1° for at least 44 hours. Approximately 2.5-g. aliquots of equilibrated solution were used for determination of the amount of dissolved sample. The purity of sample A was sufficiently low that the material gave erratic results of no analytical value in this determination. The values found and plotted in Fig. 1 are considered to be accurate within ±0.15 mg./g.

NEW YORK 11, N. Y.

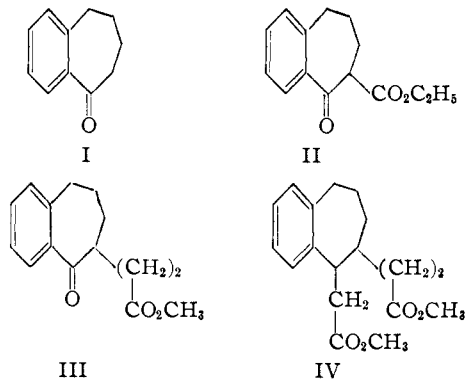
NOTES

Synthesis of Dimethyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzene-5-acetate-6-propionate[1,2]

BY A. G. ANDERSON, JR., AND HELEN FRANCES GREEF

RECEIVED APRIL 28, 1952

In the search for synthetic routes to compounds related to colchicine, we have carried out some model studies starting with 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one (I). In the course of this work dimethyl 6,7,8,9-tetrahydro-5H-cycloheptabenzene-5-acetate-6-propionate (IV) has been synthesized. IV is of interest as a model compound in that an acyloin condensation of this diester followed by bromination and dehydrobromination according to known procedures[3] would afford a third ring having a tropolone structure and the resultant ring system would then be quite similar to that present in colchicine.



Carboethoxylation of I with diethyl carbonate in the presence of sodium hydride[4] gave ethyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-carboxylate (II) in 72% yield. The sodium salt of II was prepared by reaction with sodium hydride in anhydrous dioxane. Treatment of this salt with

(1) From the Ph.D. Thesis of Helen Frances Greef.

(2) Supported in part by State of Washington Initiative 171 funds for research in biology and medicine.

(3) D. J. Cram and J. D. Knight, THIS JOURNAL, **73**, 4136 (1951).

(4) F. S. Swamer and C. R. Hauser, *ibid.*, **72**, 1352 (1950).

methyl β-bromopropionate gave an extremely viscous material which could not be obtained analytically pure but gave no test with ferric chloride and was presumed to be largely methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-carboethoxy-6-propionate. This crude material was treated with methanolic barium hydroxide[5] and the resultant acid, which decomposed on attempted purification by distillation, esterified directly with diazomethane to give methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III) as a viscous oil in 60% yield from II. Hydrolysis of the crude intermediate diester with a mixture of acetic and hydrochloric acids or with alcoholic potassium hydroxide resulted in lower yields of III and the formation of tarry by-products.

A Reformatsky reaction of III with methyl bromoacetate followed by dehydration of the crude product and then catalytic hydrogenation afforded IV in 28% over-all yield from III. The low yield realized was not unexpected as it has been previously observed[6] that hindered ketones give poor yields in the Reformatsky reaction.

Experimental[7]

Ethyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzen-5-one-6-carboxylate (II).—A solution of 160 g. (1.0 mole) of 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one (I), prepared as previously described,[8] in 300 ml. of di-*n*-butyl ether (dried over sodium hydride) was added dropwise with vigorous stirring over a period of two to three hours to a gently refluxing mixture of 48 g. (2.0 moles) of sodium hydride in 100 ml. of the dry di-*n*-butyl ether and 240 ml. of freshly distilled diethyl carbonate (b.p. 124–126°). After the addition was complete, the mixture was refluxed for six hours, during which time the mixture was kept fluid by the occasional addition of further quantities of dry solvent, and then allowed to stand overnight. After cooling to 10°, unreacted sodium hydride was destroyed by the addition of 100 ml. of alcohol and the cold mixture was then neutralized by the addition of dilute hydrochloric acid under an atmosphere of nitrogen. After separation of the layers and extraction of the aqueous layer several times with ether, the combined organic layers were washed with saturated salt solution until neutral and then dried over sodium sulfate. Distillation gave 166.5 g. (72%) of II as a yellow oil (b.p. 125–134° at 1 mm., $n^{25.5}$D 1.5623) which gave an intense purple color with 5% ferric chloride solution. The ultraviolet absorption spectrum of an ethanolic solution showed maxima in mμ at 246 (ε 6500) and 290 (ε 13,000).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.34; H, 7.00. Found: C, 72.41; H, 6.97.

Methyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III).—A solution of 156.6 g. (0.67 mole) of the aforementioned keto ester (II) in 500 ml. of purified dioxane[9] was added dropwise with stirring over a period of two to three hours to a gently refluxing mixture of 16.1 g. (0.67 mole) of sodium hydride in 100 ml. of purified dioxane. The resultant mixture was refluxed for an additional hour. To this hot mixture was then added dropwise a solution of 112 g. (0.67 mole) of methyl β-bromopropionate in 200 ml. of purified dioxane. After stirring and refluxing overnight, the mixture was cooled and the precipitated sodium bromide separated by filtration. Removal of the volatile substances from the filtrate by distillation under reduced pressure left 273.5 g. of a viscous yellow oil which gave no test with 5% ferric chloride solution but could not be purified by distillation. A mixture of 15.9 g. of this oil, presumed to contain mainly methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-carboethoxy-6-propionate, 78 g. of barium hydroxide octahydrate, 260 ml. of water and 125 ml. of methanol was refluxed vigorously for 20 hours.[5] Most of the methanol was then removed by distillation under reduced pressure and the cooled residue was acidified with dilute hydrochloric acid. The yellow oil which separated was dissolved in ether, the solution dried over sodium sulfate, and the solvent evaporated. The extremely viscous acidic yellow oil which remained (11 g.), and which decomposed on attempted purification by distillation, was taken up in 500 ml. of dry ether. This solution was cooled to 0° in an ice-bath and to it was added with stirring a cold solution of approximately 0.15 mole of diazomethane in ether. Excess diazomethane was destroyed by the addition of a few ml. of acetic acid. Distillation gave 8.56 g. (60% from II) of methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III) as a viscous yellow oil, b.p. 160–170° at 1 mm., $n^{25.5}$D 1.5344.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.39; H, 7.39.

Dimethyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzene-5-acetate-6-propionate (IV).—A mixture of 40 g. of twenty-mesh zinc, 44 g. (0.18 mole) of III, 27.5 g. (0.18 mole) of methyl bromoacetate and a crystal of iodine in 100 ml. of dry toluene was heated under reflux for three hours with the addition of 20 g. of zinc and 9.2 g. of methyl bromoacetate at one-hour intervals. After the last addition, the heating was continued for six more hours. The mixture was cooled to 0° and 100 g. of ice and 15 ml. of acetic acid added. After separation of the layers and extraction of the organic layer several times with ether, the combined organic layers were washed successively with 1% ammonium hydroxide (10–15 times), water, and a saturated sodium chloride solution, and then dried over sodium sulfate. To the brown, viscous oil which remained after removal of the solvents under reduced pressure was added 40 g. of fused, anhydrous potassium bisulfate and the mixture was heated (oil-bath) at 150–160° for one hour. The organic product was extracted from the solid material with ether, the solution dried, and the solvent removed by evaporation. The dark oil which remained was dissolved in 100 ml. of absolute methanol and treated with hydrogen at 30–40 lb. pressure in the presence of 1–2 g. of Raney nickel catalyst. After removal of the catalyst and solvent, distillation *in vacuo* gave 15.5 g. (28% from III) of IV as a viscous yellow oil, b.p. 170–180° at 0.8 mm., $n^{25.5}$D 1.5201.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 69.86; H, 7.64.

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UNIVERSITY OF WASHINGTON
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(5) G. Buchi and O. Jeger, *Helv. Chim. Acta*, **32**, 538 (1949).

(6) E. C. Horning, M. G. Horning and E. J. Platt, THIS JOURNAL, **72**, 2731 (1950).

(7) Melting points and boiling points are uncorrected.

(8) A. G. Anderson, Jr., and H. F. Greef, THIS JOURNAL, **74**, 5124 (1952).

(9) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 175.

The Synthesis of C^{14}-Labeled "Squalene"[1]

BY WILLIAM G. DAUBEN AND H. LEON BRADLOW

RECEIVED APRIL 19, 1952

The present concern in the metabolic fate of polyisoprenoid compounds[2] has revived the interest in the early hypothesis of Robinson[3] on the possibility of a direct conversion of the triterpene squalene (I) to cholesterol (II). A convenient way to test this suggestion would be to employ squalene uniquely labeled with C^{14}. The location of the label in the terpene should be such that if a conversion of the type described by Robinson occurred, the labeled atom could singly and easily be removed

(1) The term "squalene" is used to indicate that the product, although a triterpene with six double bonds, is not identical with the naturally occurring compound but is a mixture of double bond isomers (see text).

(2) "Ciba Foundation Conference on Isotopes in Biochemistry," J. and A. Churchill, Ltd., London, 1951, p. 24 ff.; K. Bloch, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., p. 111 ff.

(3) R. Robinson, *J. Chem. Soc. Ind. (London)*, **53**, 1062 (1934).