starting material for this column. This preparation gave a half-maximal response at 5×10^{-5} γ per ml. of assay medium. Ultraviolet absorption measurement showed a maximum at 281 mμ, $a^{1\%}_{1cm.}$ 428. The ratio of absorption density at 281 mμ to that at 241 mμ was 2.2. This concentrate was dissolved in 150 ml. of distilled water, and 6.58 g. of calcium chloride was added. The precipitate which formed was removed by centrifuging and washed with two 25-ml. portions of distilled water. The solution and washings were combined and applied to the column. Development was carried out with distilled water. The column was allowed to flow at the rate of 100–120 ml. per hour and one hundred ml. fractions were collected.

Progress of the column was followed by ultraviolet absorption measurements on the fractions. A highly fluorescent component having an absorption maximum at about 290 mμ appeared first. This material traveled nearly as fast as the solvent front and was completely eluted from the column by the time eleven fractions had been collected. It was closely followed by a zone having a maximum at 282 mμ and minimum at 242 mμ. This material began appearing in fraction 13 and persisted through fraction 29. It was not fluorescent. The ratio of absorption density at 282 mμ to that at 242 mμ of fraction 13 was 4.50 and remained fairly constant through fraction 27, having decreased to 4.1. Fraction 29 had a value of 3.6. At this point, the maximum shifted to lower wave lengths and fluorescence appeared in the eluate. Microbiological assay showed that activity was confined to fractions 12–33.

Crystallization of Folinic Acid.—Fractions 14–27, inclusive, from the above column, were combined and adjusted to *p*H 3.0 with 2.5 *N* hydrochloric acid. The solution was concentrated under reduced pressure to a volume of 400 ml. Crystallization occurred during the concentration. After several hours at room temperature the product was removed, washed with four 5-ml. portions of distilled water, and dried *in vacuo* over phosphoric anhydride. The product weighed 1.63 g., and gave a half-maximal response at 2.1×10^{-5} γ per ml. of assay medium. The $a^{1\%}_{1cm.}$ value at 282 mμ was 615, and at 242 mμ it was 160. The ratio of densities at these wave lengths was thus 3.84.

Properties of Folinic Acid-SF.—A sample (235 mg.) of the compound prepared as described was recrystallized by suspending in 30 ml. distilled water and adding 0.1 *N* sodium hydroxide to *p*H 6.8. The solution was filtered, acidified to *p*H 3.0, then concentrated *in vacuo* until crystallization began. After three recrystallizations in this manner the product was dried *in vacuo* over phosphoric anhydride for one hour. In the ultraviolet, $a^{1\%}_{1cm.}$ at 282 mμ was 545 and the ratio of absorption density at 282 mμ to that at 242 mμ was 4.95. A sample was dried *in vacuo* at 150° for two hours prior to analysis.

Anal. Calcd. for $C_{20}H_{23}O_7N_7$: C, 50.73; H, 4.90; N, 20.71. Found: C, 50.64; H, 5.01; N, 20.97.

The weight loss on drying was 12.3%. A second determination in which the sample was exposed to the air for about two hours gave a value of 14.7%.

The activity of this preparation was such that 1.8×10^{-5} γ per ml. of assay medium gave a half-maximal response. Folinic acid-SF decomposed without melting at 240–250° (uncor.).

AUSTIN, TEXAS
INDIANAPOLIS, INDIANA
RECEIVED OCTOBER 26, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. XII. The Partial Synthesis of 4-Pregnene-17α,20,21-triol-3-ones and Reichstein's Substance E[1]

BY PERCY L. JULIAN, EDWIN W. MEYER, WILLIAM J. KARPEL AND WAYNE COLE

Steroids having the 17α,20β,21-triol structure were obtained by the lithium aluminum hydride reduction of either 17α,21-diol-20-ones or 16,17-oxido-21-ol-20-ones, the latter yielding also the 20α-isomer. The ketonic function of 3-keto-4-pregnenes may be conveniently protected from reduction by means of enol ether formation. Thus 4-pregnene-17α,21-diol-3,20-dione 21-acetate was converted into 4-pregnene-17α,20β,21-triol-3-one while this triolone and 4-pregnene-17α,20α,21-triol-3-one were obtained from 16,17-oxido-4-pregnen-21-ol-3,20-dione 21-acetate. Cortisone acetate yielded Reichstein's substance E (4-pregnene-11β,17α,20β,21-tetrol-3-one).

In continuation of our program on the synthesis of steroids occurring in and related to those of the adrenal cortex,[1a] we became interested in certain pregnanes having the 17,20,21-triol structure. Of particular interest were Reichstein's substance E (4-pregnene-11β,17α,20β,21-tetrol-3-one) and 4-pregnene-17α,20β,21-triol-3-one (VII). This latter steroid has been reported by Ungar,[2] in his study of the adaptation syndrome, to possess a rather striking physiological activity. We are now reporting the partial synthesis of these two substances as well as that of the hitherto unknown 4-pregnene-17α,20α,21-triol-3-one (VI).

The first synthesis of 4-pregnene-17α,20β,21-triol-3-one (VII) was reported in the same year from two independent laboratories. Ruzicka and Müller[3] prepared this compound by a series of transformations beginning with $\Delta^{4,20}$-17-isopregnadien-17β-ol-3-one (17-vinyltestosterone). Logemann[4] presented a brief description of what appears to be the identical method, but details are lacking for a more exact comparison with that of the Swiss workers.

We have recently recorded the synthesis of Reichstein's substance S from 16,17-oxido-4-pregnen-21-ol-3,20-dione acetate (I).[5] The availability of this oxido steroid (I) made it an attractive intermediate for the synthesis of the triolone (VII). 16,17-Oxido-4-pregnen-21-ol-3,20-dione acetate (I) reacted smoothly with ethyl orthoformate[6] in the presence of a catalytic quantity of sulfuric acid in dioxane to produce the corresponding 3-enol ether (II) in good yield. Reduction of the enol ether (II) with lithium aluminum hydride in ether–benzene afforded a mixture of triols (III) which was best separated into its components after acid cleavage of the enol ether and acetylation. By crystallization the product was separated into two isomeric diacetates (IV and V); one melting at 189–191° (V) and the other at 251–253° (IV).

(1) Presented in part before the American Chemical Society, Chicago, Ill., Sept. 5, 1950.

(1a) For previous communication in this series, see THIS JOURNAL, **72**, 5145 (1950).

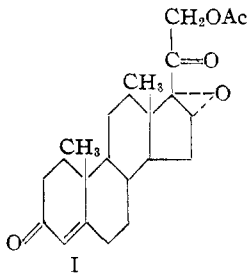
(2) G. Ungar, *Proc. Soc. Endocrinology*, **5**, liii (1947); *J. physiol. et path. gen.*, **39**, 219 (1947).

(3) L. Ruzicka and P. Müller, *Helv. Chim. Acta*, **22**, 755 (1939).

(4) Logemann, *Naturwissenschaften*, **27**, 196 (1939).

(5) Julian, Meyer, Karpel and Waller, THIS JOURNAL, **72**, 5145 (1950).

(6) Schwenk, Fleisher and Whitman, *ibid.*, **60**, 1702 (1938); Serini and Köster, *Ber.*, **71**, 1766 (1938).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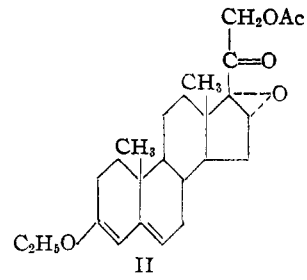
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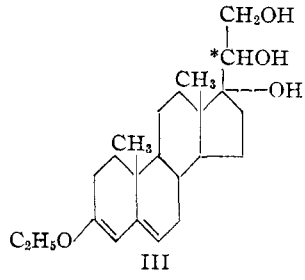
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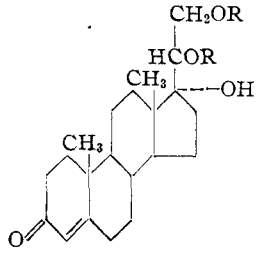
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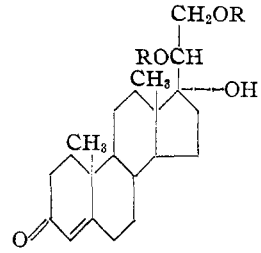
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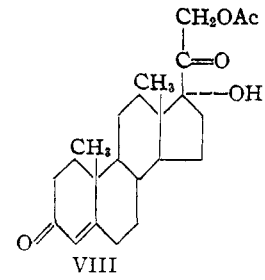
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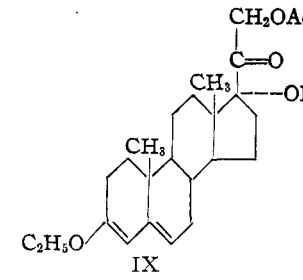
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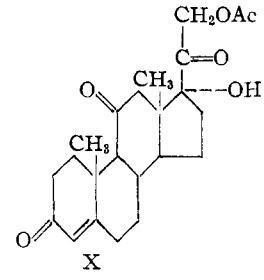
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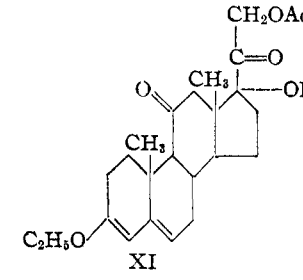
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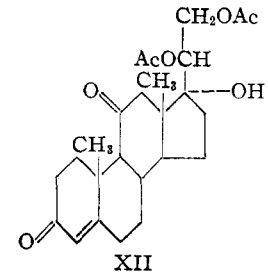
XII

The lower melting isomer proved to be identical with the 4-pregnene-17α,20β,21-triol-3-one 20,21-diacetate (V) described by Shoppee[7] and prepared by the method of Ruzicka and Müller.[8] We have assigned to the higher melting isomer the structure of the 20α-epimer, 4-pregnene-17α,20α,21-triol-3-one 20,21-diacetate (IV). This assignment is supported by the optical rotations of the two diacetates and the corresponding triolones (see accompanying table). The 253° diacetate (IV) is considerably less dextrorotatory than the known

	[M]D (chloroform) 20α	20β
Triolone (VI, VII)	+265	+293
Triolone diacetate (IV, V)	+136	+648

20β-isomer (V). Although the 20α-triolone (VI) is only slightly less dextrorotatory than the 20β-triolone (VII), acetylation causes a decrease in dextrorotation in the 20α-series and an increase in the 20β-series. These facts are in harmony with the findings of Fieser and Fieser.[8]

The simultaneous reduction of the 16,17-oxido and the 20-keto groups with lithium aluminum hydride offers an interesting contrast with the reduction of the 20-keto group in the presence of the 17α-hydroxyl group. Whereas the simultaneous reduction leads to both the 20α-ol and the 20β-ol, the lithium aluminum hydride reduction of the 17α-ol-20-one structure yielded, almost entirely, the 20β-ol. Thus when Reichstein's substance S acetate (4-pregnene-17α,21-diol-3,20-dione 21-acetate) (VIII) was converted into its 3-enol ether (IX) and reduced, there was obtained, after acetylation, in high yield, the same 4-pregnene-17α,20β,21-triol-3-one 20,21-diacetate (V) as described above. The C-20 isomeric triolone diacetate (IV) was not formed in an appreciable amount.

Reichstein's substance E was accordingly conveniently prepared by the lithium aluminum hydride reduction of the 3-enol ether (XI) of cortisone acetate (X), followed by hydrolysis of the ether. For identification it was converted into its 20,21-diacetate (XII) whose properties are identical with those described by Reichstein and von Euw.[9]

Recently several interesting facts concerning the physiological activity of 4-pregnene-17α,20β,21-triol-3-one 20,21-diacetate (V) have been reported. Dorfman[10] found that this substance inhibited comb growth, probably by direct antagonism of endogenous androgens. Terry and London[11] were unable to obtain a remission of the symptoms of rheumatoid arthritis with the administration of this steroid.

Experimental[12]

3-Ethoxy-16,17-oxido-3,5-pregnadien-21-ol-20-one Acetate (II).—A solution of 20 g. of 16,17-oxido-4-pregnen-21-ol-3-one acetate[5] in 100 ml. of dioxane and 20 ml. of ethyl orthoformate was treated at room temperature with four drops of concd. sulfuric acid in 3 ml. of dioxane. The

(7) Shoppee, *Helv. Chim. Acta*, **23**, 925 (1940).

(8) Fieser and Fieser, *Experientia*, **4**, 285 (1948); "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, Chap. V.

(9) T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **24**, 247E (1941).

(10) R. Dorfman, *Proc. Soc. Exp. Biol. Med.*, **73**, 223 (1950).

(11) L. Terry and F. London, *ibid.*, **73**, 251 (1950).

(12) Carbon-hydrogen analyses by Micro-Tech Laboratory, Skokie, Illinois. We are indebted to Isabelle Ryden Waller for certain technical assistance.

dark red solution when heated under reflux on the steam-cone deposited a mass of crystals within a short period. The mixture, after being heated for a total of one-half hour, was treated with 0.5 ml. of pyridine and concentrated *in vacuo* to a slurry. After covering it with methanol, the mixture was chilled, filtered, washed with cold methanol and dried; 17.5 g. (81%) melting at 214–218° dec. Several recrystallizations from dioxane–acetone containing a trace of pyridine gave silky white needles but did not change the melting point; $[\alpha]^{24}D$ −35.5° (21.0 mg. made up to 2 ml. with chloroform containing a drop of pyridine,[13] αD −0.373°, *l*, 1 dm.); log $\epsilon_{max.}$ 4.34 at 241 mμ in methanol.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.44; H, 8.33.

4-Pregnene-17α,20α,21-triol-3-one 20,21-Diacetate (IV) and 4-Pregnene-17α,20β,21-triol-3-one 20,21-Diacetate (V).—In a three-neck flask equipped with a mechanical agitator, dropping funnel and condenser, a suspension of 22.5 g. of lithium aluminum hydride (previously broken up rapidly in a mortar and covered with anhydrous ether) in 1,125 ml. of anhydrous ether was stirred for one-half hour and then treated with a warm solution of 45 g. of the enol ether (II) in 1,400 ml. of dry benzene. After the rapid addition, the mixture was stirred for 1 hour at room temperature and then for 2 hours at the boiling point. The mixture was then chilled in an ice-bath and cautiously decomposed with water. The ethereal layer was diluted with ethyl acetate and washed with 10% sulfuric acid followed by saline solution. The residue remaining after concentration *in vacuo* of the dried ethereal solution was dissolved in one liter of methanol, treated with 50 ml. of 2 *N* hydrochloric acid and allowed to stand at room temperature for 15 hours. The pale yellow acidic solution was then neutralized with dilute sodium bicarbonate solution and concentrated *in vacuo* to one-half volume. It was then diluted with water and extracted four times with chloroform. The combined extracts were washed once with water, dried and concentrated *in vacuo* to a waxy residue.

The mixture of triolones was acetylated with 135 ml. of acetic anhydride in 360 ml. of pyridine. After 15 hours at room temperature, the excess reagents were removed *in vacuo* and the remaining crystalline slush was slurried with methylene chloride–ether. The separated solid, after washing with ether, amounted to 11.3 g. and melted at 240–248°. The filtrate was diluted with ether and washed with 2% sulfuric acid, water, dilute sodium bicarbonate solution and water. Upon partial concentration of the dried solution a white crystalline solid separated. This material, 5.5 g., melted at 235–248° and was combined with the first fraction for purification (total yield 36%).

The solid which separated from the methylene chloride–ether solution (filtrate after separation of the 235–248° material) upon strong cooling, was filtered, washed with ether and dried; 11.6 g. melting at 189–191°. The residue after removal of solvent from the filtrate gave upon crystallization from acetone, 12.5 g. of material melting at 178–189°. This material was combined with the 189–191° fraction for recrystallization (total yield 51%).

Several recrystallizations of the higher-melting fraction from acetone gave white, fluffy needles of **4-pregnene-17α,20α,21-triol-3-one 20,21-diacetate** melting at 251–253.5°; $[\alpha]^{32}D$ +31.5° (20.3 mg. made up to 2 ml. with chloroform, αD +0.320°, *l*, 1 dm.); log $\epsilon_{max.}$ 4.24 at 241 mμ in methanol.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.52; H, 8.32.

The lower melting material when recrystallized from acetone gave heavy, colorless prisms of **4-pregnene-17α,20β,-21-triol-3-one 20,21-diacetate** melting at 189–191°, after losing solvent of crystallization at 120–130°. This material gave no depression in melting point when admixed with a sample prepared by the method of Ruzicka and Muller[3,7]; $[\alpha]^{25}D$ +150° (46.1 mg. made up to 2 ml. with chloroform, αD +3.45°, *l*, 1 dm.).

4-Pregnen-17α,20α,21-triol-3-one (VI).—A solution of 500 mg. of the diacetate (IV) in 25 ml. of methanol was treated with 500 mg. of potassium bicarbonate in 9 ml. of water. The mixture was refluxed for 2 hours, diluted with water and the solid separated; 350 mg. melting at 217–222°. Several recrystallizations from a small volume of methanol gave colorless, tabular prisms melting at 225–227.5°; $[\alpha]^{25}D$ +76.2° (20.3 mg. made up to 2 ml. with chloroform, αD +0.773°, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.27; H, 9.44.

4-Pregnene-17α,20β,21-triol-3-one (VII).—Hydrolysis of the 189–191° diacetate (V) in a fashion similar to that described for the 20α modification afforded colorless needles melting at 188–190° (solvated) after crystallization from aqueous methanol, $[\alpha]^{25}D$ +84.3° (21.2 mg. made up to 2 ml. with *chloroform*, αD +0.894°, *l*, 1 dm.); $[\alpha]^{25}D$ +65.3° (17.2 mg. made up to 2 ml. with *dioxane*, αD +0.562°, *l*, 1 dm.).[4]

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.30; H, 9.30.

3-Ethoxy-3,5-pregnadiene-17α,21-diol-20-one 21-Acetate (IX).—A suspension of 1.8 g. of 4-pregnene-17α,21-diol-3,20-dione 21-acetate (Reichstein's substance S acetate) in a mixture of 2.0 ml. of ethyl orthoformate, 0.1 ml. of anhydrous ethanol and 10 ml. of anhydrous dioxane was treated with 0.5 ml. of dioxane containing 0.025 ml. of concd. sulfuric acid and promptly swirled for about 5 minutes to effect a clear amber solution. This was allowed to stand for 20 minutes at 25°, and then 1.0 ml. of pyridine was added and the solution concentrated *in vacuo* to a sirup. The product was crystallized from 5 ml. of methanol by adding a few drops of water. The first crop, 1.61 g., m.p. 160–164°, was recrystallized from methanol containing a trace of pyridine to obtain the enol ether as colorless blades, m.p. 168°; $[\alpha]^{24}D$ −62° (22.4 mg. made up to 2 ml. with chloroform containing a drop of pyridine,[13] αD −0.70°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.92; H, 8.83.

Reduction of the Enol Ether (IX) of Substance S Acetate.—To a stirred solution of 1.4 g. of lithium aluminum hydride in 80 ml. of anhydrous ether, there was added a solution of 1.4 g. of the enol ether of substance S acetate in 30 ml. of benzene. The resulting mixture was stirred and refluxed for 2 hours and then treated with small chips of ice to decompose the excess reagent. The mixture was finally acidified with cold 5% hydrochloric acid and separated, the aqueous portion being further extracted with ether. The combined ethereal extracts were washed once with water, concentrated to about 20 ml. in volume and then diluted with 30 ml. of methanol and 5 ml. of 2% hydrochloric acid. This solution was allowed to stand for 12 hours to complete the hydrolysis of the enol ether and then concentrated *in vacuo* and extracted with ether. The dry residue from the extract was acetylated with 2 ml. of acetic anhydride in 4 ml. of pyridine during 12 hours at room temperature. The acetylation mixture was concentrated *in vacuo* to remove the majority of excess reagents and the product was crystallized by the addition of 8 ml. of anhydrous ether. A first crop of the triolone diacetate, 0.7 g. melting at 175–185°, was separated, and by reconcentrating and crystallizing the residue from ether–hexane, a second crop of 0.38 g., m.p. 169–172°, was obtained. Recrystallization from acetone raised the melting point to 190°; this material gave no depression in melting point when admixed with a sample of the material described previously.

None of the higher-melting isomer of the triolone diacetate was present in the crude product.

3-Ethoxy-3,5-pregnadiene-17α,21-diol-11,20-dione 21-Acetate (XI).—A suspension of 1.0 g. of cortisone acetate in a mixture of 1 ml. of ethyl orthoformate, 0.1 ml. of anhydrous ethanol and 7.5 ml. of anhydrous dioxane was treated with 0.035 ml. of concd. sulfuric acid in 0.7 ml. of dioxane and then swirled for about 5 minutes to obtain a clear amber solution. This was held at 26° for 10 minutes and then 0.6 ml. of pyridine was added. Water was added portionwise, with scratching, to crystallize the product which separated as buff-colored flakes, 0.9 g. melting at 191–195°. Recrystallization from methanol gave colorless plates melting at 193–194°; log $\epsilon_{max.}$ 4.42 at 242 mμ in methanol; $[\alpha]^{23}D$ +2° (21.3 mg. made up to 2 ml. with chloroform containing a drop of pyridine,[13] αD +0.024°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.72; H, 7.83.

4-Pregnene-11β,17α,20β,21-tetrol-3-one 20,21-Diacetate (XII).—To a stirred solution of 1.0 g. of lithium alu-

(13) If no pyridine is used, the rotation changes rapidly due to cleavage of the enol ether.

minum hydride in 60 ml. of anhydrous ether, there was added a solution of 0.8 g. of the enol ether of cortisone acetate in 20 ml. of benzene. The material reacted vigorously with the formation of a precipitate. After stirring and refluxing the mixture for 2 hours, small chips of ice were added to destroy the excess reagent. The mixture was then acidified with cold dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with small portions of water, and the combined aqueous fractions were salted and again extracted with ether. The ether solution was concentrated to about 10 ml. and treated with a mixture of 30 ml. of methanol and 5 ml. of 2% hydrochloric acid for 12 hours. This solution was concentrated *in vacuo* to about 5 ml. volume, salt water and ether were added and the organic layer was separated. The residue, 0.6 g. of hygroscopic tetrolone, remaining after removal of solvent from the dried ethereal solution was acetylated by treatment with 1 ml. of acetic anhydride and 3 ml. of pyridine for 10 hours at room temperature. This was then gently warmed *in vacuo* to remove excess reagents and anhydrous ether was then added to crystallize the product which separated slowly as clusters of prisms melting at 218–223°. The first crop, 0.36 g., was recrystallized several times from acetone yielding prisms, m.p. 226–227° dec. in air; m.p. 230–231° in vac.; log $\epsilon_{max.}$ 4.3 at 241 mμ in methanol; $[\alpha]^{23}D$ +163° (8.1 mg. made up to 2 ml. with acetone, αD +0.663°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.97; H, 8.09. Found: C, 66.63; H, 7.95.

CHICAGO 39, ILL. RECEIVED SEPTEMBER 21, 1950

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE JOHNS HOPKINS UNIVERSITY]

Synthetic Approaches to 1,2,3,4-Cyclobutanetetracarboxylic Acid

BY EVANS B. REID AND MILTON SACK[1]

In this paper it is shown that the alleged 1,2,3,4-cyclobutanetetracarboxylic acid is in reality fumaric acid. Attempts to prepare this cyclic acid by degradation of certain isomers of 1,3-dicarboxy-2,4-cyclobutanediacetic acids were unsuccessful. A new synthesis of ethyl 1,1,2,2,3,4-cyclobutanehexacarboxylate is described, and from this ester 1,2,3,4-cyclobutanetetracarboxylic acid, of unknown stereochemical form, has been obtained. The infrared absorption spectra of several highly substituted cyclobutanes have been determined and the characteristic cyclobutane absorptions have been noted.

In 1932 Owen and Simonsen[2] reported the formation of ethyl 1,2,3,4-cyclobutanetetracarboxylate as a *by-product* from the interaction of ethyl diazoacetate with methylheptenone in the presence of copper bronze. The same ester was again obtained when ethyl 4-methyl-3-pentenoate replaced methylheptenone in the above reaction.[3] The identification of this cyclic ester rested upon the analysis of the parent acid and the molecular weight of the methyl ester. Later, Ranganathan[4] prepared the supposed ethyl 1,2,3,4-cyclobutanetetracarboxylate, as the *main product*, from the interaction of ethyl α-isopropylacrylate with ethyl diazoacetate and copper bronze, under the conditions of Owen and Simonsen. Beyond these three reports the literature affords no other reference to this cyclic compound.

Certain stereochemical studies in this Laboratory required the preparation of 1,2,3,4-cyclobutanetetracarboxylic acid in quantity, and we therefore repeated the synthesis of Ranganathan[4] several times. However, the product, after hydrolysis, bore such a striking resemblance to fumaric acid that we were led to make a direct comparison between this unsaturated acid and the supposed 1,2,3,4-cyclobutanetetracarboxylic acid. The results of this clearly established the fact that the supposed cyclic acid of Ranganathan[4] was in reality fumaric acid. As a further check, the acid was transformed into its methyl ester by the method of Owen and Simonsen.[2] The ester proved to be methyl fumarate.[5]

Comparison of the properties of fumaric acid with those given by Owen and Simonsen[2,3] for their alleged cyclobutane acid, revealed complete agreement except for the molecular weight of the methyl ester. The English authors obtained, by the Rast method, a value very close to that calculated for the tetrabasic cyclic ester. We therefore carried out the Rast determination[6] on methyl fumarate, and obtained values approximating that of the cyclic ester, *i.e.*, nearly twice that of methyl fumarate. It is apparent that the Rast method is not reliable for this determination, probably due to strong association of the unsaturated ester. We thus are led to believe that neither 1,2,3,4-cyclobutanetetracarboxylic acid nor its esters have ever been prepared.

Turning to the question of synthesis, the most promising route to the cyclic tetracarboxylic acid, in its various forms, would appear to be through the 1,3-dicarboxy-2,4-cyclobutanediacetic acids.[7,8] Not only have all five stereoisomeric forms of the latter compound been isolated and characterized,[8] but precise conditions have been reported whereby the various forms may be interconverted.[8] Various factors, however, prevented the successful completion of these degradations. Thus, attempts to degrade the α- and β-forms of 1,3-dicarboxy-2,4-cyclobutanediacetic acid (II) (Fig. 1), in a manner analogous to that used in the case of *cis*-pinic acid,[9,10] were thwarted by the inertia of these acids toward bromination. Further, attempts to brominate the cyclic acid chloride directly[11,12] had to be abandoned since thionyl chloride yielded only the dianhydride (III). Likewise, phosphorus penta-

(1) From the doctoral dissertation of Milton Sack, The Johns Hopkins University, 1950.

(2) Owen and Simonsen, *J. Chem. Soc.*, 1424 (1932).

(3) Owen and Simonsen, *ibid.*, 1225 (1933).

(4) Ranganathan, *J. Indian Soc.*, **13**, 419 (1936).

(5) Other authors have noted the formation of fumaric esters from the decomposition of diazoesters with copper bronze catalyst, *viz.*, Loose, *J. prakt. Chem.*, [2] **79**, 505 (1909); Buchner and Schottenhammer, *Ber.*, **53**, 865 (1920).

(6) Shriner and Fuson, "The Systematic Identification of Organic Compounds," third ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 50.

(7) Guthzeit, Weiss and Schaefer, *J. prakt. Chem.*, **80**, 393 (1909).

(8) Ingold, Perren and Thorpe, *J. Chem. Soc.*, **121**, 1765 (1922).

(9) Baeyer, *Ber.*, **29**, 1908 (1896).

(10) Perkin and Simonsen, *J. Chem. Soc.*, **95**, 1174 (1909).

(11) Fourneau and Nicolotch, *Bull. soc. chim.*, **43**, 1232 (1928).

(12) Schwenk, THIS JOURNAL, **70**, 3626 (1948).