Incidental to the above experiments, there was also carried out the epoxidation of the initial degradation product Δ^{16}-allopregnene-3β,12β-diol-11-one diacetate with alkaline hydrogen peroxide. The resulting 16α,17α-oxide, isolated as the free diol, was transformed to the bromohydrin with hydrogen bromide in glacial acetic acid and immediately debrominated with palladized calcium carbonate catalyst[11] to yield allopregnane-3β,12β,17α-triol-11,20-dione.

Experimental[12]

Δ^{16}-Allopregnene-3β,12β-diol-11,20-dione Diacetate.—22a-5α-Spirostane-3β,12β-diol-11-one (I)[6] (4.9 g.) was converted into the furostene diacetate and directly oxidized with chromium trioxide and hydrolyzed with bicarbonate solution exactly as described for Δ^{7}-22a-5α-spirosten-3β-ol.[13] Chromatography through a short alumina column afforded 2.24 g. of colorless crystals with m.p. 213–215°, which upon further recrystallization from ether furnished the analytical sample with m.p. 214–216°, $[\alpha]^{20}D$ +22°, λ_{max}^{EtOH} 230 mμ (log ϵ 4.08),[14] $\lambda_{max}^{CS_2}$ 1736 (acetate) and 1680 cm.$^{-1}$ (Δ^{16}-20-ketone).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.39; H, 8.11.

Allopregnane-3β,12β-diol-11,20-dione Diacetate (IIa).—The catalytic hydrogenation of the above Δ^{16}-20-ketone (0.63 g.) was carried out in ethyl acetate solution (45 cc.) at room temperature and atmospheric pressure employing 0.11 g. of 10% palladized charcoal catalyst. The hydrogen uptake corresponding to one mole ceased within one hour, whereupon the catalyst was filtered, the filtrate evaporated to dryness and the residue was recrystallized from ether–pentane; yield 0.52 g., m.p. 155–157°, $[\alpha]^{20}D$ +29°, $\lambda_{max}^{CS_2}$ 1736 (acetate) and 1710 cm.$^{-1}$ (saturated 20-ketone).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.79; H, 8.03.

Attempts at partial saponification (limited amounts of bicarbonate at room temperature) furnished after chromatography some oily material and chiefly recovered diacetate. Potassium carbonate (room temperature or refluxing) afforded mixtures containing free diol, monoacetate and/or diacetate (free hydroxyl band as well as carbonyl bands at 1736 and 1706 cm.$^{-1}$). Saponification with boiling 5–10% methanolic potassium hydroxide yielded about 50% of solid with m.p. 147–155°, which after several recrystallizations from ether led to an analytical sample, m.p. 167–169°, $[\alpha]^{20}D$ +100°, which may be the desired diol IIb or an isomer (in ring C).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.47; H, 8.96.

16α,17α-Oxidoallopregnane-3β,12β-diol-11,20-dione.—An ice-cold solution of 0.5 g. of Δ^{16}-allopregnene-3β,12β-diol-11,20-dione diacetate in 40 cc. of methanol was treated with 1.25 cc. of 30% hydrogen peroxide followed by the addition of a solution of 0.5 g. of sodium hydroxide in 2 cc. of water. After 89 hours in the refrigerator, the solution was diluted with chloroform, washed with water until neutral, dried and evaporated. Recrystallization from acetone–hexane furnished 0.24 g. of colorless crystals with m.p. 183–185°, $[\alpha]^{20}D$ +105°, $\lambda_{max}^{CS_2}$ 1718 cm.$^{-1}$ and free hydroxyl band. The method of preparation and the physical constants do not preclude the possibility of epimerization of the ketol system in ring C.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.42; H, 8.44.

Allopregnane-3β,12β,17α-triol-11,20-dione.[15]—A solution of 2.49 g. of the above oxide in 25 cc. of glacial acetic acid was treated for 15 minutes at 18° with 5 cc. of a 32% solution of hydrogen bromide in glacial acetic acid and then diluted with much water. The bromohydrin was filtered, washed well with water, air-dried, and then hydrogenated directly with 9.0 g. of 2% palladized calcium carbonate in 75 cc. of 95% ethanol at room temperature and atmospheric pressure for 16 hours. After filtration of the catalyst and evaporation of the filtrate to dryness, the residue was allowed to stand at room temperature for two hours in 1% methanolic potassium hydroxide solution in order to saponify any 3-acetate formed during the oxide opening. Neutralization with acetic acid and concentration *in vacuo* followed by chilling afforded (two crops) 2.08 g. of crystals with m.p. 270–274°. The analytical sample was obtained from acetone and exhibited m.p. 278–282° (Fisher block), $[\alpha]^{20}D$ +52° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.29; H, 8.82.

(11) F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

(12) Melting points are uncorrected. Unless indicated otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba for the microanalyses.

(13) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(14) It is interesting to note that the ultraviolet absorption maximum is at the rather low wave length of 230 mμ, also observed with a 12-keto (ref. 9) and 8(14)-unsaturated (O. Mancera, D. H. R. Barton, G. Rosenkranz and C. Djerassi, *J. Chem. Soc.*, 1025 (1952)) Δ^{16}-20-ketone, in contrast to the expected maximum (*ca.* 238 mμ) found with the corresponding 11-ketone (ref. 10) and 12α-acetoxy derivatives (C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 660 (1949)).

(15) As pointed out above, the preparation of the oxide with alkaline hydrogen peroxide, though carried out at low temperature, may nevertheless involve isomerization of the ketol system (*cf.* ref. 5). Since the triol was obtained from the oxide, this reservation concerning the stereochemistry of the ketol system (in ring C) applies to both substances.

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Condensation of Trisodium Tricarballylate with Propionic Anhydride

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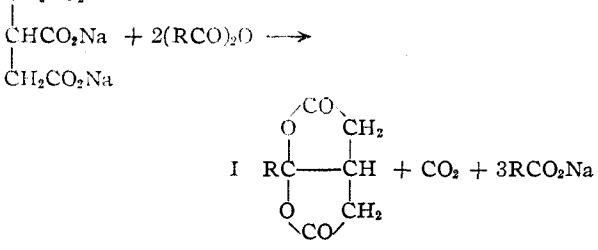
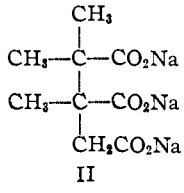
The condensation of trisodium tricarballylate with an acid anhydride to form a β-acylglutarobislactone (I) appears to be a fairly general reaction.[1,2] The method has been applied successfully to acetic anhydride,[3] *n*-butyric anhydride,[4] isobutyric anhydride,[4] benzoic anhydride[5] and phthalic anhydride.[6] The yields of I ranged from 5 to 43%. The position of condensation, at the site of the central carboxyl group of trisodium tricarballylate, was proved beyond question.



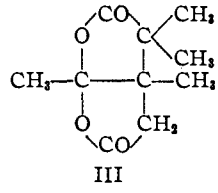
Trisodium camphoronate (II) has also been reported to form β-aceto-α,α,β-trimethylglutarobislactone (III) by reaction with acetic anhydride.[7]

The bislactones I were reported to undergo hydrolysis to β-acylglutaric acids IV on being boiled

(1) R. Fittig, *Ber.*, **30**, 2145 (1897).
(2) R. Fittig, *Ann.*, **314**, 1 (1901).
(3) R. Fittig and E. Roth, *ibid.*, **314**, 16 (1901).
(4) R. Fittig and T. Guthrie, *ibid.*, **314**, 40 (1901).
(5) R. Fittig and H. Salomon, *ibid.*, **314**, 58 (1901).
(6) R. Fittig and O. Gottsche, *ibid.*, **314**, 74 (1901).
(7) R. Fittig and H. Salomon, *ibid.*, **314**, 89 (1901).

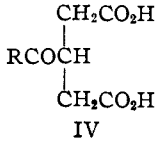


II

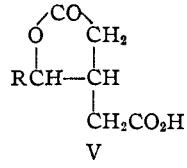


III

with water. The bislactones I could also be reduced by means of sodium amalgam to γ-alkyl-γ-butyrolactone-β-acetic acids V, but yields were not specified.[2,8]



IV



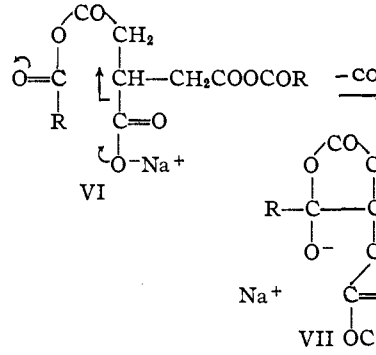
V

Since the condensation reaction of trisodium tricarballylate with propionic anhydride had never been reported, and since we desired the unknown γ-caprolactone-β-acetic acid (V, R = C_2H_5) as an intermediate for another project, we investigated the condensation reaction and subsequent reduction. β-Propionylglutarobislactone (I, R = C_2H_5) was obtained in 80% yield in the condensation step. To avoid the cumbersome sodium amalgam method of reduction, we reduced β-propionylglutarobislactone by means of sodium borohydride,[9] γ-caprolactone-β-acetic acid (V, R = C_2H_5) being obtained in 93% yield. Although two racemates for the acid are theoretically possible, only one pure substance was isolated from the reduction. This parallels the experience of the earlier workers.[1-8]

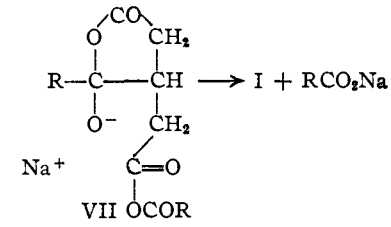
β-Propionylglutarobislactone was hydrolyzed to β-propionylglutaric acid (IV, R = C_2H_5), which was converted to ethyl β-propionylglutarate. A reduction of the ester with sodium borohydride afforded a good combined yield of γ-caprolactone-β-acetic acid and its ethyl ester. Ethyl γ-caprolactone-β-acetate could also be prepared from the corresponding acid either by direct esterification or *via* the acid chloride.

There has existed some doubt as to whether structure I is correct for the anhydrides of the β-acylglutaric acids IV.[8] An alternate structure to be considered is the keto anhydride. To settle this question, the infrared spectrum of β-propionylglutarobislactone (I, R = C_2H_5) was determined. It possesses a single absorption band in the carbonyl region, at 5.60 μ. This indicates with considerable certainty that structure I is correct.

With regard to the mechanism of the condensation reaction of trisodium tricarballylate with an acid anhydride, we suggest that a mixed anhydride is first formed, in which the two terminal carboxyl groups are converted to anhydride groups in preference to the more highly hindered central carboxyl group. Then, by way of the five-membered "ring" transition, VI, a molecule of carbon dioxide is lost and a new carbon-to-carbon bond is formed, giving VII.[10] Finally, VII undergoes further ring closure to I.



VI



VII

The best available evidence indicates that the decarboxylative acylation which takes place in the Dakin–West reaction of α-amino acids and arylacetic acids involves acylation at the α-position of the acid (actually an intermediate azlactone or anhydride) prior to decarboxylation.[11] This mechanism obviously requires the α-amino acid or arylacetic acid to have at least one α-hydrogen. The same mechanism cannot apply to the reaction of trisodium camphoronate with acetic anhydride to give III. By analogy, it is probable that the reaction of trisodium tricarballylate with an acid anhydride to give I also does not involve this mechanism.

Acknowledgment.—This work was supported in part by a grant from the Office of Naval Research.

Experimental[12]

Trisodium Tricarballylate.—To 400 cc. of water containing 40.0 g. (1.0 mole) of sodium hydroxide was added 58.0 g. (0.33 mole) of tricarballylic acid.[13] The solution was evaporated to dryness on the steam-bath. The residue was ground to a fine powder and dried to constant weight in a vacuum oven at 45°, 80.0 g.

Reaction of Trisodium Tricarballylate with Propionic Anhydride.—To 80.0 g. of trisodium tricarballylate in a 250-cc. flask fitted with a thermometer well, a condenser and a calcium chloride drying tube was added 80.0 g. of freshly distilled propionic anhydride. The mixture was heated on an oil-bath at 130°, the reaction mixture itself being maintained at 120°. An immediate evolution of carbon dioxide was observed. At intervals of two hours, 30.0-g. portions of propionic anhydride were added until a total of 192.0 g. (1.47 moles) was used. The mixture turned light brown, and at the end of 50 hours, the evolution of carbon dioxide stopped. The mixture solidified on cooling. The solid mass was triturated with seven 200-cc. portions of low-boiling Skellysolve, followed by six 150-cc. portions of chloroform. On evaporation of the combined Skellysolve, chloroform extracts, some crystalline β-propionylglutarobislactone formed and was filtered. The filtrate was subjected to distillation at 10 mm. pressure, and distillate up to b.p. 62° was rejected. The residue in the flask

(8) W. O. Emery, *Ann.*, **295**, 94 (1897).

(9) (a) A. M. Soldate, THIS JOURNAL, **69**, 987 (1947); (b) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949); (c) H. Heymann and L. F. Fieser, *ibid.*, **73**, 525 2(1951); (d) R. P. Zelinski, B. W. Turnquest and E. C. Martin, *ibid.*, **73**, 5521 (1951).

(10) There are other recorded examples of decarboxylation reactions in which the fragment remaining after loss of carbon dioxide adds to a carbonyl carbon atom. (a) P. Dyson and D. Ll. Hammick, *J. Chem. Soc.*, 1724 (1937); (b) M. R. F. Ashworth, R. P. Daffern and D. Ll. Hammick, *ibid.*, 809 (1939); (c) B. R. Brown and D. Ll. Hammick *ibid.*, 173, 659 (1949); (d) M. S. Schechter, N. Green and F. B. LaForge, THIS JOURNAL, **71**, 1517 (1949); (e) G. Stork and H. Conroy, *ibid.*, **73**, 4743 (1951).

(11) (a) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928); (b) G. H. Cleland and C. Niemann, THIS JOURNAL, **71**, 841 (1949); (c) J. A. King and F. H. McMillan, *ibid.*, **73**, 4911 (1951); (d) S. Searles and G. J. Cvejanovich, *ibid.*, **72**, 3200 (1950).

(12) Analyses by Weiler and Strauss, Oxford, England. Infrared spectra by Samuel P. Sadtler and Son, Inc., Philadelphia, Pa. All m.ps. are corrected.

(13) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 538.

consisted of β-propionylglutarobislactone and some sodium propionate. The bislactone was extracted with chloroform, and on addition of ice-cold low boiling Skellysolve, the bislactone crystallized.

A total of 45.0 g. (0.27 mole) of bislactone was obtained, 80%. It was easily purified by dissolving it in a minimum of anhydrous acetone and adding a few drops of anhydrous ether. It crystallized as colorless needles, m.p. 62.0–62.5°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.78, 56.82; H, 6.18, 6.24.

The infrared absorption spectrum showed a single absorption maximum in the carbonyl region, at 5.60 μ, in nujol mull.

β-Propionylglutaric Acid.—To 150 cc. of water was added 19.3 g. of β-propionylglutarobislactone, and the solution was refluxed for 18 hours. Water was distilled *in vacuo*. The residual sirup solidified on trituration with low boiling Skellysolve, 19.0 g., m.p. 82–87°. Colorless crystals were obtained from anhydrous toluene, m.p. 87–88°.

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.20, 51.51; H, 6.37, 6.23.

Ethyl β-Propionylglutarate.—A mixture of 40.0 g. (0.21 mole) of β-propionylglutaric acid, 200 cc. of absolute ethanol, 100 cc. of benzene and 20 cc. of concentrated sulfuric acid was distilled through an 18″ electrically heated Vigreux column to which was attached an azeotropic distillation head. When only one liquid phase appeared in the condensed distillate and the temperature of the overhead vapor reached 68°, the distillation was stopped. Most of the remaining benzene and alcohol was distilled *in vacuo* and the residue neutralized with sodium bicarbonate. The mixture was extracted with ether and dried over anhydrous sodium sulfate. The ether was distilled and the crude ester fractionated. After a slight forerun there was obtained 41.0 g. (79%) of ethyl β-propionylglutarate, b.p. 121–122° (0.2 mm.).

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.61; H, 8.27.

The infrared spectrum of the liquid showed a somewhat broad absorption band at 5.81 μ. There was a small shoulder at 5.60 μ, probably indicating the presence of a trace of β-propionylglutarobislactone as impurity.

A higher boiling fraction in the above distillation consisted of 1.5 g. of β-propionylglutarobislactone, b.p. 137° (0.2 mm.), m.p. 62.0–62.5°.

Reduction of β-Propionylglutarobislactone with Sodium Borohydride.—To a solution of 53.0 g. (0.312 mole) of the bislactone in 250 cc. of water containing 11 g. of potassium hydroxide was added 12.0 g. of sodium borohydride in small portions during three hours. The reaction was carried out in an erlenmeyer flask with stirring by a magnetic stirrer. The mixture was stirred for an additional six hours, then allowed to stand 12 hours more. The mixture was acidified with 6 *N* hydrochloric acid, then extracted with ether in a continuous extraction apparatus for 48 hours. γ-Caprolactone-β-acetic acid crystallized in the ether flask, 50.0 g. (93%). Colorless crystals were obtained from toluene, m.p. 98.0–98.4°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 56.03, 56.78; H, 7.15, 7.15.

Reduction of Ethyl β-Propionylglutarate with Sodium Borohydride.—To a solution of 55.0 g. (0.23 mole) of ethyl β-propionylglutarate in 180 cc. of ethanol was slowly added a solution of 5.4 g. of sodium borohydride in 180 cc. of ethanol and 37 cc. of 2 *N* sodium hydroxide solution. The reaction mixture was mechanically stirred during the addition of the sodium borohydride solution and for 15 minutes thereafter. A white complex which had formed was dissolved by addition of 55 cc. of water, and the solution was stirred for three hours, with occasional warming on the steam-bath. The solution was filtered and the alcohol distilled *in vacuo*. The aqueous alkaline solution was acidified and thoroughly extracted with ether. The ether solution was dried over anhydrous sodium sulfate.

Fractionation of the organic layer gave 14.5 g. (31%) of ethyl γ-caprolactone-β-acetate, b.p. 133–136° (0.08 mm.), $n^{30}D$ 1.4525.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.88; H, 8.06. Found: C, 59.77, 59.75; H, 8.33, 8.53.

The infrared spectrum of ethyl γ-caprolactone-β-acetate showed carbonyl absorption bands at 5.63 and 5.80 μ.

A second major fraction from the distillation consisted of 15.0 g. (38%) of γ-caprolactone-β-acetic acid, b.p. 175–180° (0.03–0.05 mm.), m.p. 98.0–98.4°.

Ethyl γ-Caprolactone-β-acetate. A. *Via* **the Acid Chloride.**—To 20.0 g. of γ-caprolactone-β-acetic acid in a flask fitted with a stirrer and reflux condenser was added dropwise 14.0 g. of thionyl chloride. The mixture was refluxed on the steam-bath for an additional hour. The unreacted thionyl chloride was removed by distillation, then 25 cc. of absolute ethanol was added and the mixture refluxed on the steam-bath for one hour. Ethanol was distilled *in vacuo*, and the residue was fractionated. There was obtained 22.0 g. (94%) of ethyl γ-caprolactone-β-acetate, b.p. 135° (0.09 mm.).

B. **Azeotropic Esterification.**—The reaction was carried out in the same manner as that described for ethyl β-propionylglutarate. From 50.0 g. of γ-caprolactone-β-acetic acid there was obtained 48.0 g. (83%) of the ester.

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N,N′-Dialkyloxamides[1]

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RECEIVED OCTOBER 9, 1952

In the course of another investigation we have prepared the series of symmetrical N,N′-dialkyloxamides through octadecyl, with the exception of heptadecyl. The oxamides were obtained in excellent yields by the reaction of 2 moles of a primary amine with one mole of ethyl oxalate. In all cases the compounds formed readily at room temperature and separated in a high state of purity. Several members of the series had been previously prepared in isolated cases.

The derivatives may be formed in an aqueous alcohol medium in contrast to acid chlorides and aryl isocyanates which are not water stable. Ethyl oxalate, besides being readily available, is not readily affected by water. In addition, this reagent may be used to separate mixtures of primary, secondary and tertiary amines, as the last two are unreactive with ethyl oxalate under the conditions employed.

TABLE I

N,N′-DIALKYLOXAMIDES, R—NHC(=O)—C(=O)—NH—R

R	Formula	M.p., °C.	Nitrogen, % Calcd.	Found
Butyl	$C_{10}H_{20}N_2O_2$	153–154	13.99	14.08
Amyl	$C_{12}H_{24}N_2O_2$	141–142	12.27	11.82
Hexyl	$C_{14}H_{28}N_2O_2$	134–135	10.93	10.71
Heptyl	$C_{16}H_{32}N_2O_2$	132–132.5	9.85	9.45
Octyl	$C_{18}H_{36}N_2O_2$	124–125	8.97	8.93
Nonyl	$C_{20}H_{40}N_2O_2$	128–129	8.23	8.33
Decyl	$C_{22}H_{44}N_2O_2$	122–123	7.60	7.97
Hendecyl	$C_{24}H_{48}N_2O_2$	124–125	7.06	7.33
Dodecyl[a]	$C_{26}H_{52}N_2O_2$	123–124	6.59	6.67
Tridecyl	$C_{28}H_{56}N_2O_2$	120–121	6.19	6.29
Tetradecyl[b]	$C_{30}H_{60}N_2O_2$	117.5–119	5.82	5.98
Pentadecyl	$C_{32}H_{64}N_2O_2$	120	5.51	5.42
Hexadecyl[b]	$C_{34}H_{68}N_2O_2$	117–118	5.22	5.02
Octadecyl	$C_{38}H_{76}N_2O_2$	118–120	4.72	4.54

[a] Grunfeld, *Compt. rend.*, 194, 893 (1932). [b] S. P. Massie, *Iowa State Coll. J. Sci.*, 21, 41 (1946).

(1) Supported in part by a grant from the Geschickter Fund for Medical Research, Inc.

(2) Professor Emeritus, Johns Hopkins University, Baltimore, Md.