of the catalytic hydrogenation product of Ia (m.p. 166–168°; Marker, *et al.*,[3a] give m.p. 120°) and the infrared spectra were identical. The diacetate differed from chlorogenin diacetate (m.p. 155–156°) as evidenced by a depression in m.p. on admixture and differences in the infrared spectra.

Δ^{16}-Allopregnene-3β,6β-diol-20-one Diacetate (III).—A mixture of 10 g. of the diacetate IIb and 50 cc. of acetic anhydride was heated in an autoclave at 185–190° for 8 hours, poured into water, extracted with ether, washed well with sodium carbonate solution, dried and evaporated. The resulting oily "furosten" was oxidized with chromium trioxide and the resulting "diosone" subjected to saponification as described previously.[12] Chromatographic purification on alumina and crystallization from ether–pentane afforded 5.11 g. (63%) of the allopregnene derivative III with m.p. 164–165°, $[\alpha]_D$ −18°, λ_{max} 238 mμ, log ϵ 4.03, ν_{max} 1718 and 1660 cm.$^{-1}$ (reported[8] m.p. 233–235°).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.38; H, 8.58.

Allopregnane-3β,6β-diol-20-one Diacetate (IV).—The Δ^{16}-compound III (1.20 g.) dissolved in 100 cc. of ethyl acetate was hydrogenated over 0.4 g. of 5% palladium–charcoal at atmospheric pressure and room temperature. After 2 hours, the catalyst and solvent were removed and the residue was crystallized from ether–pentane. The resulting allopregnane-3β,6β-diol-20-one diacetate (0.96 g.) showed m.p. 175–177°, $[\alpha]_D$ +18°, no appreciable absorption in the ultraviolet, ν_{max} 1718 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.45; H, 8.89.

$\Delta^{16,20}$-Allopregnadiene-3β,6β,20-triol Triacetate (Enol Acetate of III).—A solution of 8.0 g. of the Δ^{16}-derivative III and 1.5 g. of *p*-toluenesulfonic acid in 180 cc. of isopropenyl acetate was slowly distilled during the course of 10 hours (120 cc. of distillate collected). Addition of water, followed by extraction with ether, washing with sodium carbonate, drying and evaporation left a residue which on crystallization from ether–pentane yielded 7.1 g. (81%) of the enol acetate with m.p. 169–172°. The analytical sample showed m.p. 179–181°, $[\alpha]_D$ +36°, λ_{max} 238 mμ, log ϵ 4.18, ν_{max} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.98; H, 8.53.

Δ^{16}-Allopregnene-3β,6β,21-triol-20-one Triacetate (VIb).—The above enol acetate (6.9 g.) was heated with 6.9 g. of N-iodosuccinimide in 40 cc. of dioxane at 80° for 2 hours. Addition of water, extraction with ether (ether layer washed with sodium thiosulfate and water) and crystallization from methanol afforded 6.7 g. of the iodoketone VIa with m.p. *ca.* 200° (dec., varies with rate of heating), λ_{max} 250 mμ, log ϵ 3.94, ν_{max} 1718 and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}O_5I$: C, 55.33; H, 6.51. Found: C, 55.01; H, 6.60.

The iodoketone was refluxed with 20 g. of potassium acetate in 200 cc. of acetone for 6 hours, and was then poured into water. Ether extraction and crystallization from ether–pentane furnished 4.8 g. (54% over-all based on III) of the unsaturated triacetate VIb with m.p. 137–138°, λ_{max} 240 mμ, log ϵ 4.20.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.48; H, 8.24.

Allopregnane-3β,6β,21-triol-20-one Triacetate (V). (a) From Allopregnane-3β,6β-diol-20-one Diacetate (IV).—A solution of 0.80 g. of the saturated diacetate IV and 1.5 g. of lead tetraacetate (Arapahoe Chemicals, Boulder, Colo.; *ca.* 90% pure) in 20 cc. of glacial acetic acid was heated on the steam-bath for 6 hours and then left at room temperature overnight. The solution was poured into water, the product was isolated with ether and chromatographed on 30 g. of neutral alumina. Crystallization of the fractions eluted with hexane–benzene from ether–pentane yielded 0.44 g. (48%) of the triacetate V with m.p. 138–140°, $[\alpha]_D$ +25°, ν_{max} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.10; H, 8.12.

(b) From Δ^{16}-Allopregnene-3β,6β,21-triol-20-one Triacetate (VIb).—The unsaturated triacetate VIb (2.0 g.) dissolved in 40 cc. of ethyl acetate was hydrogenated over 0.4 g. of a 5% palladium–charcoal catalyst at room temperature and atmospheric pressure. Crystallization of the product from ether–pentane afforded 1.81 g. (90%) of the saturated triacetate V with m.p. 137–139°, $[\alpha]_D$ +23°, no appreciable absorption in the ultraviolet. Identity with the sample prepared by method (a) was established through mixture m.p. determination and infrared comparison.

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

Steroids. LIX.[1] Ring D Rearrangement of 17α,-21-Dihydroxy-20-ketosteroids

BY E. BATRES, G. ROSENKRANZ AND FRANZ SONDHEIMER

RECEIVED APRIL 28, 1954

The so-called "D-homo" rearrangement of 17α-hydroxy-20-ketosteroids of the pregnane series (type Ia) to the corresponding 17aα-hydroxy-17aβ-methyl-17-keto-D-homoandrostane derivatives (type IIa) has been effected stereospecifically through heat treatment and through reaction with aluminum alkoxides and with boron trifluoride–acetic acid–acetic anhydride (to yield the 17aα-acetates).[2,3] Moreover this isomerization may be brought about by the action of potassium hydroxide, which however yields the 17a-isomer of IIa as the major product.[3] The D-homo rearrangement has not been carried out previously with compounds of type Ib, possessing the 17α-hydroxy-21-acetoxy-20-keto side chain characteristic of cortisone acetate. We were interested in performing the isomerization with compounds of this series so as to make available reference substances which could be compared with microbiological transformation products.[4]

17α-Hydroxydesoxycorticosterone (Reichstein's substance S) 21-acetate (Ib) was subjected to Oppenauer oxidation conditions (boiling with aluminum isopropoxide and cyclohexanone in toluene). The product, isolated in 46% yield, was assigned the 17aβ-acetoxymethyl-17aα-hydroxy-17-keto-D-homoandrostane structure IIb, since analysis proved it to be isomeric with the starting material, and since similar conditions (aluminum *t*-butoxide in benzene with or without acetone) in the 21-desoxy series had led to the corresponding 17aβ-methyl-17aα-hydroxy-17-keto compounds (type IIa).[2] In agreement with this formulation, the rearranged acetate IIb gave a negative reaction with triphenyltetrazolium chloride,[5] although the saponification product IIc reacted weakly positively.

(1) Steroids. LVIII, J. Romo, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 5169 (1954).

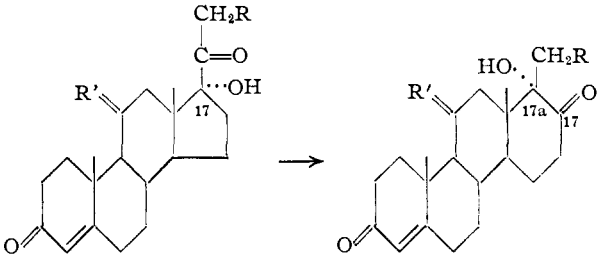
(2) *Inter al.*, P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941); R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).

(3) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

(4) *Cf.* J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952). Added in proof: V. Georgian and N. Kundu [*Chemistry and Industry*, 431 (1954)] have now described the D-homo rearrangement of Substance S Acetate and of cortisone acetate with boron trifluoride–acetic acid–acetic anhydride.

(5) This test in the steroid series has been found so far to be specific for compounds containing the 21-hydroxy-20-keto function either in the free or esterified form (*cf.* A. Zaffaroni, "Recent Progress in Hormone Research," Academic Press, Inc., New York, N. Y., Vol. VIII, 1953, p. 77,

Similarly cortisone acetate (III) and hydrocortisone (17α-hydroxycorticosterone) acetate (V) were isomerized to the corresponding D-homo compounds IV and VI. The latter two substances could be inter-related, for oxidation of the 11β-hydroxy group of VI with chromic acid yielded the cortisone acetate rearrangement product IV. It was to be expected that the 11β-hydroxy function would be unaffected during the rearrangement of hydrocortisone acetate (V) to VI, since it is known that the 11β-hydroxy grouping is not attacked to any appreciable extent under the Oppenauer oxidation conditions employed.[6]



Ia, R = H, R′ = <H/H IIa, R = H, R′ = <H/H

Ib, R = OAc, R′ = <H/H IIb, R = OAc, R′ = <H/H

IIc, R = OH, R′ = <H/H

III, R = OAc, R′ = O IV, R = OAc, R′ = O

V, R = OAc, R′ = <OH(β)/H VI, R = OAc, R′ = <OH(β)/H

In Table I (upper part) the molecular rotation values of the D-homo steroids of type IIb, reported in this paper, are compared with the 17α-hydroxy-21-acetoxy-20-ketones from which they are derived. It is apparent that in each case the rearrangement is accompanied by a comparatively small negative shift in the molecular rotation. This effect is in contrast to the rather large negative shift observed in the 21-desoxy series on passing from 17α-hydroxy-20-ketones to D-homo compounds of type IIa (Table I, lower part).

TABLE I

MOLECULAR ROTATION DATA FOR D-HOMO STEROIDS (TYPES IIa AND IIb)[a]

	$[M]_D$	$[M]_D^{Homo}$	$\Delta[M]_D$
17α-Hydroxydesoxycorticosterone (substance S) 21-acetate	+554[b]	+520[c]	−34
17α-Hydroxydehydrocorticosterone (cortisone) 21-acetate	+820[d]	+768[c]	−52
17α-Hydroxycorticosterone (hydrocortisone) 21-acetate	+630[e]	+606[c]	−24
Allopregnane-3β,17α-diol-20-one (substance L) 3-acetate (in acetone)	+ 68[f]	−118[g]	−186
Δ⁵-Pregnene-3β,17α-diol-20-one 3-acetate (in dioxane)	−153[h]	−378[i]	−225
Δ⁴-Pregnen-17α-ol-3,20-dione (17α-hydroxyprogesterone)	+348[j]	+218[j]	−130

[a] Rotations were determined in chloroform solution unless indicated otherwise. [b] Determined in these laboratories. [c] This paper. [d] J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952). [e] J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953). [f] G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950). [g] L. Ruzicka, K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **22**, 626 (1939). [h] P. Hegner and T. Reichstein, *ibid.*, **24**, 828 (1941). [i] C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 201 (1943).

(6) *Cf.* G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

Experimental[7]

17aβ-Acetoxymethyl-D-homo-Δ⁴-androsten-17aα-ol-3,17-dione (IIb).—A solution of 5 g. of Reichstein's substance S 21-acetate (Ib) and 1.25 g. of aluminum isopropoxide in 200 cc. of carefully dried toluene was refluxed with 40 cc. of cyclohexanone for 1 hour, moisture being excluded. The cooled mixture was poured into water, the organic solvents were removed by steam distillation, and the product was extracted with ethyl acetate. Washing the organic extract with water, drying and evaporation yielded a clear oil, which slowly crystallized. It was purified through chromatography on 250 g. of neutral alumina. The fractions eluted with benzene–ether on crystallization from acetone–ether furnished 2.28 g. (46%) of the rearrangement product IIb with m.p. 188–191°. The analytical sample was obtained by further crystallization from the same solvent pair, and showed m.p. 194–196°, $[\alpha]^{20}D$ +134°, λ_{max} 240 mμ (log ε 4.22), ν_{max} 1736, 1700 and 1670 cm.$^{-1}$ and free hydroxyl band. The reaction with triphenyltetrazolium chloride was negative.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.27; H, 8.60.

The free diol IIc was obtained by mixing an ice-cold solution of 0.50 g. of the acetate IIb in 20 cc. of methanol with 1.5 cc. of a methanol solution containing 0.15 g. of potassium hydroxide previously dissolved in a few drops of water, under a nitrogen atmosphere. The mixture was allowed to stand at room temperature for 1 hour; it was then acidified with acetic acid, evaporated *in vacuo* to a volume of *ca.* 5 cc., cooled, and a few drops of water were added. The diol IIc (0.43 g., 97%), m.p. 188–190°, was collected and crystallized from acetone–hexane. The analytical specimen exhibited m.p. 193–194°, $[\alpha]^{20}D$ +122°, λ_{max} 240 mμ (log ε 4.23), ν_{max} 1700 and 1670 cm.$^{-1}$ and free hydroxyl band. The compound gave a weak positive reaction with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.78; H, 8.37.

17aβ-Acetoxymethyl-D-homo-Δ⁴-androsten-17aα-ol-3,11,-17-trione (IV).—The rearrangement was carried out with 5 g. of cortisone 21-acetate (III) through refluxing with 1.25 g. of aluminum isopropoxide in 280 cc. of toluene and 40 cc. of cyclohexanone as described above for the 11-desoxy series. The product was chromatographed on 250 g. of neutral alumina, and the crystalline fractions eluted with benzene–ether and with ether were crystallized from methanol. The rearranged triketone IV (1.57 g., 31%) thus obtained showed m.p. 195–198°. A sample further purified by crystallization from methanol–chloroform exhibited m.p. 199–201°, $[\alpha]^{20}D$ +191°, λ_{max} 237 mμ (log ε 4.20), ν_{max} 1736, 1710 and 1670 cm.$^{-1}$ and free hydroxyl band. The reaction with triphenyltetrazolium chloride was negative.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.41; H, 7.68.

17aβ-Acetoxymethyl-D-homo-Δ⁴-androstene-11β,17aα-diol-3,17-dione (VI).—Kendall's compound F (hydrocortisone) 21-acetate (V) (1 g.) was rearranged through 1-hour refluxing with 0.25 g. of aluminum isopropoxide in 600 cc. of toluene and 15 cc. of cyclohexanone, as described above. Chromatographic purification of the resulting oil on 50 g. of neutral alumina and crystallization of the fractions eluted with ether from acetone–ether furnished 0.41 g. (41%) of the rearranged triol monoacetate VI, m.p. 173–176°. The analytical sample was obtained by crystallization from the above-mentioned solvent pair and showed m.p. 181–183°, $[\alpha]^{20}D$ +150°, λ_{max} 240 mμ (log ε 4.23), ν_{max} 1736, 1700 and 1666 cm.$^{-1}$ and free hydroxyl band. The reaction with triphenyltetrazolium chloride was negative.

(7) Melting points are uncorrected. Rotations were measured in chloroform, and ultraviolet absorption spectra in 95% ethanol solution. Infrared spectra were determined in chloroform solution with a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. We are grateful to Mrs. P. Lopez for these measurements and to Miss A. Barba for the microanalyses.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.06; H, 7.70.

There was a strong depression in m.p. on admixture with the corresponding 11-ketone IV, and the infrared spectra were different.

Oxidation of VI to IV.—The oxidation of 100 mg. of the hydrocortisone acetate rearrangement product VI was carried out with 50 mg. of chromium trioxide in 10 cc. of acetic acid for 10 minutes at room temperature. Isolation with chloroform and crystallization from methanol yielded the triketone IV, m.p. 196–200°, identified with the material (m.p. 199–201°) obtained from cortisone acetate by mixture m.p. determination and infrared comparison.

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Derivatives of 2-Phenylbenzimidazole. II

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As a continuation of work reported earlier[2] all twelve of the 5-nitro-2-monohalophenylbenzimidazoles have been prepared. The data for the derivatives are given in Table I. The method used in the preparation of these compounds was essentially that of Walther and v. Pulawski.[3] The *o*- and *p*-chloro derivatives were prepared also by the method of Weidenhagen[4] using the appropriate halobenzaldehyde, cupric acetate and 4-nitro-*o*-phenylenediamine. The yields were 17 and 45%, respectively.

In addition the three 2-monofluorophenylbenzimidazoles were prepared using the same method as previously reported.[1] The data for these compounds are given in Table II.

Experimental

4-Nitro-*o*-phenylenediamine (0.013 mole) and the appropriate halobenzoic acid (0.013 mole) were heated in a Pyrex tube at 210–220° in an oil-bath for one hour. The cooled mass was pulverized, triturated with a saturated solution of sodium bicarbonate, filtered and the residue extracted with hot ethanol. The product was obtained from the alcohol solution by the addition of water. Repeated crystallization from aqueous ethanol using charcoal gave analytically pure samples in the yields indicated in Table I.

The *o*-fluoro-, *o*-chloro- and *o*-bromonitro derivatives were white crystalline substances, while the *o*-iodonitro compound was light yellow. All of the other halonitro derivatives were yellow crystalline substances. The *p*-fluoro- and *o*-chloronitro compounds turned yellow on heating and melted to give a yellow liquid. The *o*-bromo isomer melted to give a yellow liquid while the *o*-iodo isomer turned white on heating but melted to give a yellow liquid. The three 2-fluorophenylbenzimidazoles were white crystalline substances. All of the derivatives were insoluble in water but soluble in acetone, ether, dioxane and alcohol.

TABLE I

4-Nitro-*o*-phenylenediamine condensed with, acid	Yield, %	M.p., °C.[a]	Formula	Nitrogen,[b] % Calcd.	Found	Halide,[c] % Calcd.	Found
o-Fluorobenzoic	21	189	$C_{13}H_8FN_3O_2$	16.33	16.58	7.4	7.4
m-Fluorobenzoic	18	208			16.21		7.2
p-Fluorobenzoic	9	260			16.55		7.7
o-Chlorobenzoic	11	181	$C_{13}H_8ClN_3O_2$	15.38	15.35	13.0	12.7
m-Chlorobenzoic	13	223			15.76		12.5
p-Chlorobenzoic	10	308			15.14		12.7
o-Bromobenzoic	5	173	$C_{13}H_8BrN_3O_2$	13.20	13.55	25.2	24.6
m-Bromobenzoic	10	226			13.62		24.7
p-Bromobenzoic	7	294			13.58		24.7
o-Iodobenzoic	4	208	$C_{13}H_8IN_3O_2$	11.50	11.32	34.8	35.1
m-Iodobenzoic	11	230			11.23		34.9
p-Iodobenzoic	10	264			11.78		34.9

[a] All melting points were determined by means of a Fisher–Johns hot-stage, melting point block. [b] Micro-Dumas nitrogen analyses by C. F. Geiger, 312 Yale St., Ontario, California. [c] Halogen analyses, except fluorine, after fusion in a micro-peroxide bomb were by Volhard titration. Fluorine analyses after fusion in a peroxide bomb were by the method of Nichols and Olsen.[5]

TABLE II

o-Phenylenediamine condensed with, acid	Yield, %	M.p., °C.[a]	Formula	Nitrogen[a] % Calcd.	Found	Halide,[a] % Calcd.	Found
o-Fluorobenzoic	26	207	$C_{13}H_9FN_2$	13.21	13.14	9.0	9.3
m-Fluorobenzoic	46	258			13.57		9.6
p-Fluorobenzoic	39	257			13.94		8.5

[a] See notes to Table I.

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Isomaltose Phenylosazone and Phenylosotriazole

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The phenylosazone of a crude "isomaltose" has been described by Fischer[2] and others.[3] The

(1) This work was supported by a grant from the Research Corporation.

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(1) Research Associate of the Corn Industries Research Foundation.

(2) E. Fischer, *Ber.*, **23**, 3687 (1890); **28**, 3024 (1895).

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