Table I. — Relative percentage of the electrophoretic components of soluble proteins of lymphatic tissue in normal, adrenalectomized and fasted rats (means ± S.E.M.).

Condition	Pools analyzed n.	Electrophoretic components					
		a	*b*	*c*	*d*	*e*	*f*
Normals	5	2·39 ± 0·17	13·11 ± 1·08	63·25 ± 2·19	11·89 ± 1·66	5·73 ± 0·52	4·06 ± 1·34
Adrenalectomized . . .	5	1·78 ± 0·14*	8·97 ± 0·81*	67·14 ± 1·55	11·13 ± 0·57	6·73 ± 1·03	2·49 ± 1·50
Fasted for 96 h.	3	1·70 ± 0·26	11·43 ± 0·27	62·66 ± 2·15	16·40 ± 0·52	5·97 ± 1·12	3·20 ± 1·01

* Differences with normals statistically significant ($P < 0.05$; Student's test).

were clearly separated. They had a mobility respectively of 14·4 and 9·6 × 10^{-5} cm^2 volt/s. Since at the end of the run, they were not present in the electrophoretic pattern, their percentage is not included in the data of Table I.

The final electrophoretic pattern is reproduced in the Figure. 6 components identified with the letters from *a* to *f* are apparent, of which *c* is quantitatively the most important, corresponding to more than 60% of the total proteins. The mobilities of these components are tabulated in Table II.

From Table I it is evident that no qualitative modifications took place in the patterns from adrenalectomized or fasted rats in comparison with the normals. From a quantitative point of view, the analysis of soluble proteins from adrenalectomized rats showed a statistically significant percentage decrease of components *a* and *b* in comparison with the normals.

Table II.—Mobilities of electrophoretic fractions of soluble proteins of lymphatic tissue

Fraction . . .	*a*	*b*	*c*	*d*	*e*	*f*
Mobility* . . .	6·07	5·58	4·59	3·28	2·54	1·64

* × 10^{-5} cm^2 $volt^{-1}$ s^{-1}.

Soluble proteins of normal lymphatic tissue have been studied by ABRAMS and COHEN[5] and by ROBERTS and WHITE[6], who found 6–7 components with a wide range of mobilities. In extracts of isolated lymphocytes, WHITE and DOUGHERTY[7] and HARRIS, MOORE, and FARBER[8] found 6–7 or respectively 3 components. Our results are therefore in broad agreement with those of the previous authors.

The main result of the present investigation is that in the experimental conditions employed, in which lymphatic tissue undergoes marked weight and morphological variations, very small or no modifications are appreciable in the electrophoretic patterns of the soluble proteins. This is particularly striking in the case of fasting, when the loss of lymphocytes is great and the lymphatic organs appear to be constituted mainly of reticulo-endothelial cells.

After adrenalectomy, where an increase of the lymphocytes content of the tissues is evident, two small fast components show a statistically significant decrease. It seems appropriate to recall here that WHITE and DOUGHERTY[7] found, in lymphocytes, isolated from lymph nodes draining territories in which an antigen had been injected, an increase in the fast electrophoretic components. These results seem, therefore, to indicate a correlation between these fast components and the functional activity of lymphocytes (presumably increased after the injection of the antigen and decreased after adrenalectomy).

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Zusammenfassung

Elektrophoresediagramme von löslichen Proteinen des lymphatischen Gewebes wurden geprüft unter zwei experimentellen Bedingungen, die Gewichtsveränderungen des lymphatischen Gewebes in entgegengesetzten Richtungen bewirkten (rascher Gewichtsverlust bei Hungertieren und Gewichtszunahme nach Adrenalektomie).

Im Vergleich mit Kontrolltieren zeigten die Elektrophoresediagramme unter diesen Versuchsbedingungen keine qualitativen Veränderungen. Nur nach Adrenalektomie war die Konzentration zweier kleiner Komponenten signifikant geringer als bei Normaltieren.

[5] A. ABRAMS and P. P. COHEN, J. biol. Chem. *177*, 439 (1949).
[6] S. ROBERTS and A. WHITE, J. biol. Chem. *178*, 151 (1949).
[7] A. WHITE and T. F. DOUGHERTY, Endocrinology *36*, 207 (1945).
[8] T. N. HARRIS, D. H. MOORE, and M. FARBER, J. biol. Chem. *179*, 369 (1949).

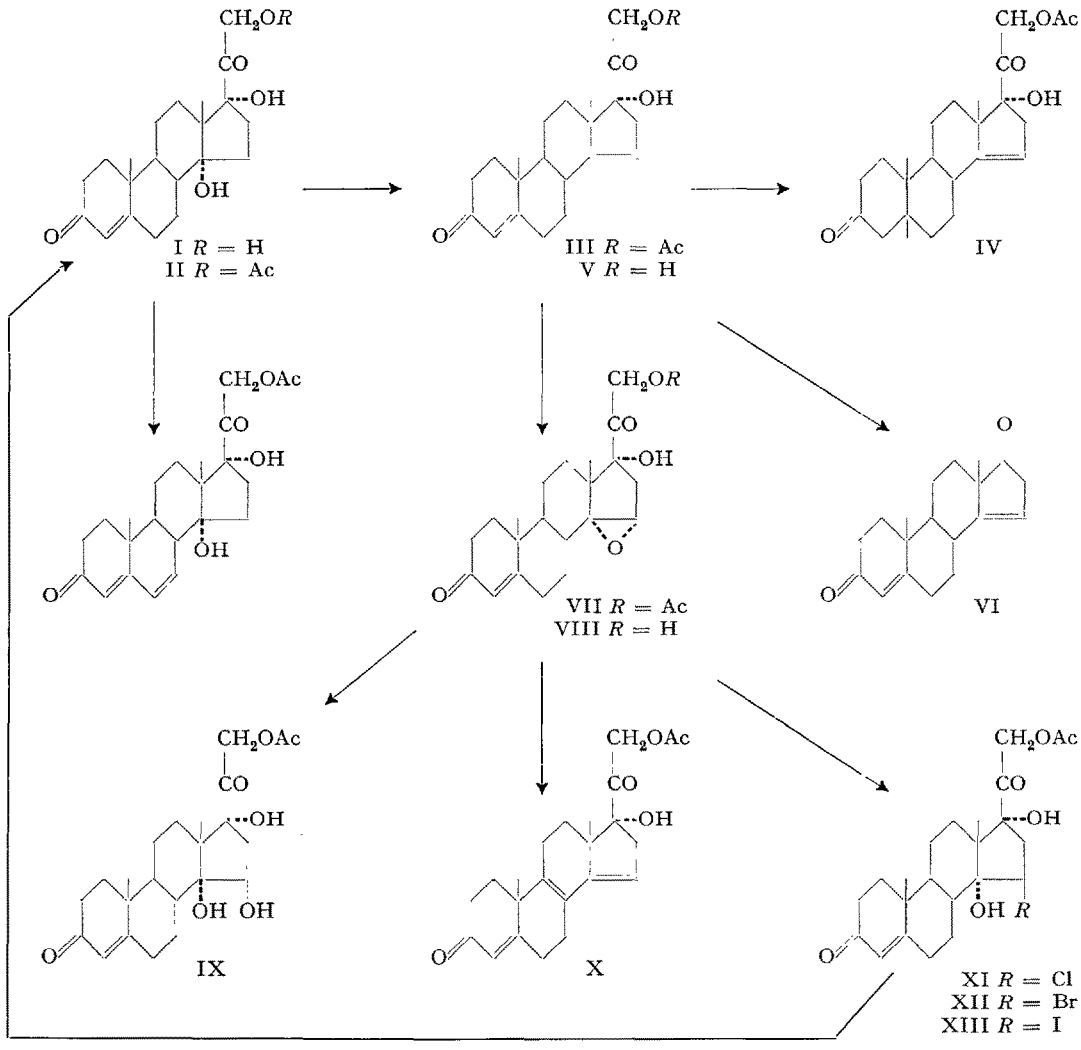
$C_{(14)}$-Substituted Corticosteroids. Some D Ring Transformations in the Compound S Series

The current interest in substituted analogs of cortisone and hydrocortisone as anti-inflammatory agents has recently been stimulated by the reported synthesis of several compounds displaying heightened glucocorticoid activity as well as markedly divergent mineralocorticoid properties[1]. In searching for new therapeutic agents of this type, we have prepared as model compounds several $C_{(14)}$-substituted derivatives of Reichstein's Compound S. The synthesis of the corresponding 11-oxygenated compounds and their biological activities has been reported elsewhere[2].

The preparation of $C_{(14)}$-substituted derivatives of Compound S was accomplished from Δ^4-pregnene-14α, 17α, 21-triol-3, 20-dione (14α-hydroxy Compound S)

[1] J. FRIED *et al.*, J. Amer. chem. Soc. *75*, 2273 (1953); *76*, 1455 (1954); *77*, 1068 (1955); *77*, 4181 (1955). – A. NOBILE *et al.*, J. Amer. chem. Soc. *77*, 4184 (1955). – R. F. HIRSCHMANN, R. MILLER, R. E. BEYLER, L. H. SARETT, and M. TISHLER, J. Amer. chem. Soc. *77*, 3166 (1955). – J. A HOGG *et al.*, J. Amer. chem. Soc. *77*, 4438 (1955). – E. VISCHER, CH. MEYSTRE, and A. WETTSTEIN, Helv. chim. Acta *38*, 835 (1955).

[2] E. J. AGNELLO, B. M. BLOOM, and G. D. LAUBACH, J. Amer. chem. Soc. *77*, 4684 (1955); Abstracts of 128th Meeting, Amer. Chem. Soc., Minneapolis, Minn., September 11–16, 1955, p. 50.



(I)[3]. Acetylation of I with acetic anhydride-pyridine gave the 21-monoacetate II which could be selectively dehydrated with *p*-toluenesulfonic acid in refluxing benzene to afford in excellent yield $\Delta^{4,14}$-pregnadiene-17α,21-diol-3,20-dione acetate (III), m.p. 201·4–202·8°; $[\alpha]_D$ + 75° (dioxane); ε EtOH/240 = 16,200; λ KBr/max 3·05, 5·74, 5·82, 6·09, 6·25, 8·13; (*Anal.* Calculated for $C_{23}H_{30}O_5$: C, 71·5; H, 7·82. Found: C, 71·7; H, 8·02). The formation of even trace amounts of the corresponding $\Delta^{8(14)}$-isomer was not detected in this reaction[4]. This tendency of 14α-hydroxy steroids upon dehydration to yield $C_{(14)}$-$C_{(15)}$ unsaturated products to the apparent exclusion of the isomeric $\Delta^{8(14)}$-olefins represents a notably specific elimination reaction also observed in the 17-keto[5]- and desoxycorticosterone[6] series. It might be expected from the favorably planar transition state geometry involved [8βH(*p*), 14αOH(*p*)] that the $\Delta^{8(14)}$-isomer would be the predominant product in such dehydrations. Actually the prevailing situation probably resembles that suggested by COREY[7] to explain the unusual stability toward base of 6-keto-7α-bromosteroids, where the bulky axial methyl groups at $C_{(10)}$ and $C_{(13)}$ hinder the successful removal of a proton from $C_{(8)}$ by solvent or a base[8]. Models reveal that the 15β-

[3] H. C. MURRAY and D. H. PETERSON, U.S. 2,602,769, July 8, 1952; U.S. 2,673,866, March 30, 1954. – P. D. MEISTER *et al.*, Abstracts of Papers, 123rd Amer. Chem. Soc. Meeting, Los Angeles, Calif., March 15–19, 1953, p. 5C.

[4] Treatment of II with anhydrous hydrogen chloride in chloroform at 0° also led to III.

[5] A. F. ST. ANDRÉ, H. B. MACPHILLAMY, J. A. NELSON, A. C. SHABICA, and C. R. SCHOLZ, J. Amer. chem. Soc. *74*, 5506 (1952). – Activated 14α-hydroxyl functions are known to dehydrate readily toward $C_{(15)}$ under mild acidic conditions. *Cf.* G. D. LAUBACH, E. C. SCHREIBER, E. J. AGNELLO, E. N. LIGHTFOOT, and K. J. BRUNINGS, J. Amer. chem. Soc. *75*, 1514 (1953). – N. L. MCNIVEN, J. Amer. chem. Soc. *76*, 1725 (1954). – A. ZÜRCHER, H. HEUSSER, O. JEGER, and P. GEISTLICH, Helv. chim. Acta *37*, 1562 (1954).

[6] Private communication from Dr. HOWARD RINGOLD of Syntex, S.A.

[7] E. J. COREY, J. Amer. chem. Soc. *76*, 175 (1954).

[8] Even in the case of a 14α-hydroxysteroid where the 8β-hydrogen enjoys ketonic activation, facile dehydration to form a $C_{(8)}$-$C_{(14)}$-double bond is not observed. The product of *N*-bromosuccinimide halogenation of II (Δ^4-6-bromopregnene-14α,17α,21-triol-3,20-dione acetate, m.p. 128·8–129·9° (dec.); Calculated for $C_{23}H_{31}O_6Br$: Br, 16·34%. Found: Br, 16·34%) upon refluxing with *s*-collidine affords $\Delta^{4,6}$-pregnadiene-14α,17α,21-triol-3,20-dione acetate, m.p. 223·2–223·8°, $[\alpha]_D$ + 51° (dioxane); ε EtOH/283 = 28,100; λ KBr/max 3·02, 3·14, 5·74, 5·82, 6·10, 6·22, 6·34, 8·21, 11·38; (*Anal.* Calculated for $C_{23}H_{30}O_6$: C, 68·6; H, 7·51. Found: C, 68·7; H, 7·58). During these experiments we have not detected the characteristic ultraviolet chromophore of the conjugated trienone which might be expected to arise under such vigorous conditions *via* base-catalyzed elimination of water in the vinylogous β-hydroxy ketone.

hydrogen is considerably less subject to steric effects of this type in the dehydration of 14α-hydroxysteroids.

Attempts to reduce the isolated double bond in III revealed a marked resistance of this unsaturation to catalytic hydrogenation[9], in contrast to the readily reducible "β"-anhydro (Δ^{14}) compounds prepared from cardiac aglycones[10]. Although the presence of a neighboring 17-hydroxyl group on the "α"-face could presumably account for this observation as due to steric hindrance, the necessity remained for unequivocal demonstration that the newly introduced unsaturation in III was between $C_{(14)}$ and $C_{(15)}$. This was accomplished by degradation of the cortical side chain to afford the corresponding 17-ketosteroid. Saponification of III with dilute methanolic potassium carbonate gave $\Delta^{4,14}$-pregnadiene-17α, 21-diol-3, 20-dione (V), m.p. 196·8—198·8°; $[\alpha]_D$ + 52° (dioxane); ε EtOH/240 = 16,100; λ KBr/max 2·98, 5·85, 6·04, 6·22; (*Anal.* Calculated for $C_{21}H_{28}O_4$: C, 73·2; H, 8·19. Found: C, 72·9; H, 7·97). Side chain cleavage of V with sodium bismuthate[11] afforded $\Delta^{4,14}$-androstadiene-3, 17-dione (VI), m.p. 138·8–140·8°; $[\alpha]_D$ + 246° ($CHCl_3$); ε EtOH/237 = 15,600; λ KBr/max 5·78, 6·04, 6·23; (*Anal.* Calculated for $C_{19}H_{24}O_2$: C, 80·2; H, 8·50. Found: C, 80·1; H, 8·39)[12]. When subjected to catalytic hydrogenation over 25% palladium on calcium carbonate, VI rapidly absorbed *two moles* of hydrogen producing what appeared to be a mixture of the two $C_{(5)}$-isomeric, 14β-tetrahydro compounds[13], m.p. 171—175°; $[\alpha]_D$ + 97° ($CHCl_3$); λ KBr/max 5·82, 5·88; no selective absorption in the ultraviolet region; (*Anal.* Calculated for $C_{19}H_{28}O_2$: C, 79·1; H, 9·79. Found: C, 78·9; H, 9·71).

Epoxidation of III with perphthalic acid or sodium dichromate in aqueous acetic acid[15] led to Δ^4-14α, 15α-epoxidopregnene-17α, 21-diol-3, 20-dione acetate (VII)[16], m.p. 178·2–179·2°; $[\alpha]_D$ + 119·6° (dioxane); ε EtOH/237 = 17,700; λ KBr/max 2·92, 5·74 (shoulder), 5·79, 6·03, 6·22, 8·10; (*Anal.* Calculated for $C_{23}H_{30}O_6$: C, 68·6; H, 7·51. Found: C, 68·4; H, 7·46)[17]. Saponification afforded the parent alcohol VIII, m.p. 229·6–232·2°; $[\alpha]_D$ + 135° (dioxane); ε EtOH/239 = 17,400; λ KBr/max 2·94, 5·83, 6·09, 6·23; (*Anal.* Calculated for $C_{21}H_{28}O_5$: C, 70·0; H, 7·83. Found: C, 69·7; H, 7·50).

Although stable to the action of moderately acidic reagents[18], the epoxide VII reacted readily with strong acids leading to a number of transformation products. Perchloric acid in aqueous acetone solution[19] effected hydrolytic scission of the epoxide linkage yielding a mixture of compounds. Chromatographic separation afforded a glycol tentatively formulated as Δ^4-pregnene-14α, 15β, 17α, 21-tetrol-3, 20-dione acetate (IX), m.p. 250·8–253·2°; $[\alpha]_D$ + 114° (dioxane); ε EtOH/242 = 17,400; λ KBr/max 3·00, 3·07, 5·71, 5·88, 6·04, 6·24, 8·20; (*Anal.* Calculated for $C_{23}H_{32}O_7$: C, 65·7; H, 7·67. Found: C, 65·5; H, 7·64). Selective dehydrative cleavage of the epoxide VII with *p*-toluenesulfonic acid in refluxing benzene solution led to $\Delta^{4,8,14}$-pregnatriene-17α, 21-diol-3, 20-dione acetate (X), m.p. 184·6–188·0°; ε EtOH/241 = 28,600; λ KBr/max 2·99, 5·76, 5·81, 6·05, 6·19, 6·36, 8·13.

The action of anhydrous hydrogen chloride in chloroform on VII at 0° for four hours afforded Δ^4-15β-chloropregnene-14α, 17α, 21-triol-3, 20-dione acetate (XI), m.p. 196·8–200·2° (dec.); $[\alpha]_D$ + 89° (dioxane); ε EtOH/240 = 16,550; λ KBr/max 2·98, 3·16, 5·72, 5·82, 6·16, 6·27, 8·19; (*Anal.* Calculated for $C_{23}H_{31}O_6Cl$: C, 62·9; H, 7·12; Cl, 8·08. Found: C, 62·7; H, 7·07; Cl, 8·21). Anhydrous hydrogen bromide in chloroform at – 15° for 1 h produced Δ^4-15β-bromopregnene-14α, 17α, 21-triol-3, 20-dione acetate (XII) in either of two polymorphic modifications displaying markedly different infrared spectra in potassium bromide suspension, but identical spectra in chloroform solution, m.p. 159·4–162·4° (dec.) or 175·0–177·0° (dec.); $[\alpha]_D$ + 34° (dioxane); ε EtOH/238 = 16,270; λ $CHCl_3$/max 2·96, 5·76, 5·80, 6·05, 6·22; (*Anal.* Calculated for $C_{23}H_{31}O_6Br$: C, 57·1; H, 6·46; Br, 16·3. Found: C, 57·3; H, 6·52; Br, 17·0). The epoxide VII in chloroform solution reacted with 48% hydriodic acid at 5° for 20 min to give Δ^4-15β-iodopregnene-14α, 17α, 21-triol-3, 20-dione acetate (XIII)[20], m.p. 128·4–131·2° (dec.); $[\alpha]_D$-22° (dioxane); ε EtOH/237 = 18,000; λ KBr/max 2·99, 5·74, 5·80, 6·10, 6·21, 8·11; (*Anal.* Calculated for $C_{23}H_{31}O_6I$: C, 52·1; H, 5·89; I, 23·93. Found: C, 51·8; H, 5·77; I, 25·28.) Supporting evidence for the 14α-

[9] Hydrogenation of III over 25% palladium on calcium carbonate in dioxane or ethanol gave Δ^{14}-pregnene-17α, 21-diol-3, 20-dione acetate (IV), m.p. 154·2–154·8°; $[\alpha]_D$ + 15° (dioxane); λ KBr/max 3·05, 5·72, 5·82, 5·93, 8·13; no selective absorption in the ultraviolet region; (*Anal.* Calculated for $C_{23}H_{32}O_5$: C, 71·1; H, 8·30. Found: C, 71·1; H, 8·35). Similarly platinum oxide in acetic acid failed to effect saturation of the D ring.

[10] H. M. E. Cardwell and S. Smith, J. chem. Soc. *1954*, 2012.

[11] C. J. W. Brooks and J. K. Norymberski, Biochem. J. *55*, 371 (1953).

[12] Dr. St. André of CIBA has kindly provided us with the unpublished constants [Chem. Rev. *53*, 114 (1953)] of a sample of VI prepared from 3β-acetoxy-$\Delta^{5,14}$-androstadiene-17-one[8]. This sample displayed: m.p. 137–139°; $[\alpha]_D$ + 249° ($CHCl_3$); ε_{239} = 16,377.

[13] Since androstanedione melts at 132–133° and etiocholanedione melts at 132–134°, while 14-isoandrostanedione[14] melts at 184–186°; $[\alpha]_D$ + 110° ($CHCl_3$); it seems likely that only β-face hydrogenation has occurred at $C_{(14)}$.

[14] A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, J. Amer. chem. Soc. *74*, 5506 (1952).

[15] The formation of identical epoxidation products from highly substituted olefins using either peracids or chromate oxidizing agents has been observed frequently [*cf.* H. Reich and A. Lardon, Helv. chim. Acta *30*, 329 (1947). – C. W. Shoppee, Helv. chim. Acta *30*, 766 (1947)]. A recent example in the terpene series is cited by J. D. Johnston and F. S. Spring, J. chem. Soc. *1954*, 1556.

[16] Preferential α-face attack by bulky reagents in the steroid series is thoroughly documented. *Cf.* L. F. Fieser, Exper. *6*, 312 (1950). – Pl. A. Plattner *et al.*, Helv. chim. Acta *29*, 2023 (1946). – T. F. Gallagher and T. H. Kritchevsky, J. Amer. chem. Soc. *72*, 882 (1950). – G. H. Alt and D. H. R. Barton, J. chem. Soc. *1954*, 1356. – P. Bladon, J. chem. Soc. *1954*, 736.

[17] In both Zaffaroni and Bush paper chromatographic systems, VII displayed a remarkable *Rf* value, being markedly *less polar* than Compound S acetate. We attribute this behavior to a shielding effect of the epoxide oxygen, preventing effective contact of the more polar 17α-hydroxyl grouping with the absorbing surface.

[18] Unsuccessful attempts were made to cleave the epoxide linkage in VII with boiling acetic acid [J. Pataki, G. Rosenkranz, and C. Djerassi, J. Amer. chem. Soc. *73*, 5375 (1951). – A. Fürst and Pl. A. Plattner, Helv. chim. Acta *32*, 275 (1949)], thiocyanic acid [E. E. van Tamelen, J. Amer. chem. Soc. *73*, 3444 (1951)], pyridine hydrobromide [P. N. Chakravorty and R. H. Levin, J. Amer. Chem. Soc. *64*, 2317 (1942)], thiourea and *p*-toluenesulfonic acid [L. C. King and J. A. Campell, J. Amer. chem. Soc. *71*, 3556 (1949)], magnesium bromide etherate [W. E. Bachmann, J. P. Horwitz, and R. J. Warzynski, J. Amer. chem. Soc. *75*, 3268 (1953). – R. B. Turner, J. Amer. chem. Soc. *75*, 3484 (1953)], and trichloroacetic acid in benzene [A. Fürst and R. Scotoni, Jr., Helv. chim. Acta *36*, 1410 (1953)].

[19] *Inter al.*, S. A. Julia and H. Heusser, Helv. chim. Acta *35*, 2080 (1952).

[20] More vigorous reaction conditions resulted in the formation of III as the predominant product. The reduction of steroid epoxides to the parent olefins by hydriodic acid has been previously observed. [J. Fried *et al.*, J. Amer. chem. Soc. *75*, 2273 (1953);

hydroxy-15β-halo formulation is derived from the observation that the halohydrins are converted back to the parent oxide with potassium acetate in ethanol, while the bromohydrin afforded II upon treatment with Raney nickel[21] under carefully defined conditions. Zinc dust in acetic acid[22] at room temperature converted XII to III, but unchanged starting material was recovered when XII was allowed to react with potassium iodide in refluxing acetone[23]. The chlorohydrin XI was not attacked by chromic acid.

In those steroid olefins where the direction of attack by bulky electrophilic reagents is rigidly determined by steric factors (*inter al.*: $\Delta^{9(11)}$-and Δ^{11}-compounds), the addition of hypobromous acid followed by elimination of the elements of hydrogen bromide has invariably led to epoxides[24] isomeric with those resulting from direct peracid oxidation. Attempts to apply such a procedure to the D-ring olefin III provided unusual results which we attribute to participation of the neighboring cortical side chain. When III was allowed to react with *N*-bromoacetamide in aqueous dioxane containing perchloric acid, the product isolated directly was a *halogen-free* compound XIV, m.p. 242·4–245·8° w.p.s.; $[\alpha]_D$ + 23° (dioxane); εEtOH/237 = 17,900; λKBr/max 2·93, 5·77, 5·94, 6·04, 6·21, 8·13; (*Anal.* Calculated for $C_{23}H_{30}O_6$: C, 68·6; H, 7·51. Found: C, 68·7; H, 7·65). The infrared spectrum of XIV displayed no additional hydroxyl or carbonyl bands and this fact considered along with the unreactiveness of the compound toward perphthalic acid and the chromic acid-pyridine complex[25] led to the conclusion that the newly introduced oxygen atom was present in a cyclic ether linkage. The reaction of XIV with anhydrous hydrogen chloride in chloroform for 4 h at 0° gave a chlorohydrin XV, m.p. 177·4–179·2° (dec.); $[\alpha]_D$ + 101° (dioxane); εEtOH/240 = 16,750; λKBr/max 2·96, 5·71, 5·85, 6·06, 6·21, 8·13; (*Anal.* Calculated for $C_{23}H_{31}O_6Cl$: C, 62·9; H, 7·12; Cl, 8·08. Found: C, 63·0; H, 7·14; Cl, 7·97). The chlorohydrin could be recovered unchanged after treatment with chromic anhydride in acetic acid, *suggesting the absence of a secondary hydroxyl function.* The possibility that a skeletal rearrangement had occurred during the preparation of the chlorohydrin was excluded by converting back to XIV with potassium acetate in refluxing ethanol. Further structure studies on the cyclic ether XIV and related compounds are underway.

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Research Laboratories Chas. Pfizer and Co., Inc., Brooklyn 6, N. Y., September 21, 1955.

Zusammenfassung

Eine Anzahl am D-Ring substituierter Derivate von Reichsteins Verbindung S wurde als Modellverbindungen in der Synthese neuer Corticosteroide hergestellt. Die beschriebenen Strukturtypen schliessen Dehydroverbindungen, Epoxyde, Halogenhydrine und ein Glykol ein.

[21] P. L. JULIAN *et al.*, J. Amer. chem. Soc. *72*, 5145 (1950). – L. B. BARKLEY, M. W. FARRAR, W. S. KNOWLES, and H. RAFFELSON, J. Amer. Chem. Soc. *76*, 5017 (1953). – J. SCHMIDLIN and A. WETTSTEIN, Helv. chim. Acta *36*, 1241 (1953). – G. P. MUELLER, R. E. STOBAUGH, and R. S. WINNIFORD, J. Amer. chem. Soc. *75*, 4888 (1953). – J. W. CORNFORTH, J. M. OSBOND, and G. H. PHILLIPS, J. chem. Soc. *1954*, 907.

[22] L. F. FIESER and X. A. DOMINGUEZ, J. Amer. chem. Soc. *75*, 1704 (1953).

[23] J. FRIED *et al.*, J. Amer. chem. Soc. *75*, 2273 (1953).

[24] J. FRIED *et al.*, J. Amer. chem. Soc. *75*, 2273 (1953). – G. H. OTT and T. REICHSTEIN, Helv. chim. Acta *26*, 1799 (1943).

[25] G. I. POOS, G. E. ARTH, R. E. BEYLER, and L. H. SARETT, J. Amer. chem. Soc. *75*, 422 (1953).

Leukozytenemigrationsfördernde Wirkung von Crotonöl

In einer früheren Arbeit haben wir beschrieben, dass unter den entzündungserregenden Stoffen das Crotonöl insofern eine besondere Stellung einnimmt, als dieses neben starker lokaler Reizwirkung und Entzündungserregung eine hochspezifische, chemotaktische und leukozytenwanderungsfördernde Wirkung *in vitro* besitzt[1]. Es ist seit längerem von BERENBLUM[2] beschrieben worden, dass Crotonöl eine tumorrealisierende Wirkung hat. Diese Frage wurde in letzter Zeit von DANNEEL[3] bearbeitet, der zeigen konnte, dass die entzündungserregenden Anteile nicht diejenigen sind, welche eine tumorrealisierende Wirkung besitzen. SICÉ und Mitarbeiter[4] konnten weiterhin zeigen, dass unter anderem Alkoholextrakte zu Hauthyperplasie, aber nicht zu Hautschäden führen. Es schien bei dieser Situation interessant, den Versuch zu machen, die chemotaktisch wirksamen Stoffe mit den anderen Wirkungen in Zusammenhang zu bringen. Es war versprechend, die gleichen Fraktionen wie DANNEEL zu untersuchen. Auf unsern Wunsch war DANNEEL so freundlich, uns die entsprechenden Fraktionen zur Verfügung zu stellen. Diese konnten ebenfalls verglichen werden mit den in unserer chemischen Abteilung von A. MARXER hergestellten Fraktionen, über deren Untersuchungen wir im einzelnen später berichten werden. Wir haben die von DANNEEL uns zur Verfügung gestellten Fraktionen sowohl auf ihre Leukozytenwirkung wie auch auf ihre Reizwirkung an der Konjunktiva des Kaninchens untersucht. Es ergab sich, dass vor allen Dingen zwei Fraktionen eine Wirkung auf Leukozyten besitzen; die eine hat zudem eine ausgesprochene entzündungserregende bzw. Reizwirkung. Diese Fraktion findet sich im Chloroformextrakt 3*a*, 3*b* und 3*c*, wobei 3*c* die wirksamste Unterfraktion zu sein scheint. Die zweite Fraktion mit leukotaktischer Wirkung findet sich in der Alkoholfraktion, die keine oder nur eine sehr geringe Reizwirkung besitzt. Die vorstehenden Untersuchungen ergeben somit, dass die Reizwirkung und die Leukozytenwirkung in einer Fraktion gemeinsam vorhanden sind, in der Alkoholfraktion aber nur die Leukozytenwirkung vorliegt. Es ist noch nicht zu schliessen, dass die chemotaktischen Stoffe dieser beiden Fraktionen identisch sind. Auf Grund der Danneelschen und Sicéschen Untersuchungen im Vergleich zu unseren kann gesagt werden, dass die tumorrealisierende Wirkung mit grosser Wahrscheinlichkeit mit der auf Leukozyten wirksamen Substanz nicht identisch ist und dass die Leukozytenwirkung sich in gewissen Fraktionen abtrennen lässt von den reizenden und hautschädigenden Komponenten. Es bestätigen somit diese Befunde unsere eigenen früheren Feststellungen[5], dass im Crotonöl hochwirksame, spezifisch

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