[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Antispasmodics. I. 2-Diethylaminoethyl Esters of α-Substituted 2-Thienylacetic and β-(2-Thienyl)-propionic Acids*

BY FREDERICK LEONARD

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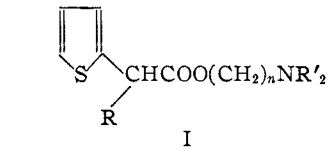
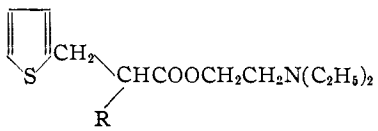
A series of basic alkyl esters of the general formula 2-$C_4H_3S(CH_2)n(R)CHCOOCH_2CH_2N(C_2H_5)_2$·HCl has been prepared for evaluation as antispasmodics. The most effective members of the series were those compounds wherein n is 0 and R is a 2-cyclopenten-1-yl or 2-cyclohexen-1-yl group. Those esters in which the 2-thienyl group is separated from the acetic acid residue by a methylene group are much less potent than the corresponding compounds in which the 2-thienyl radical is attached directly to the acetic acid moiety.

The systematic search for synthetic antispasmodics started about twenty years ago when the synthesis, for testing as spasmolytics, was first undertaken of esters related to, but simpler in structure, than atropine (*i.e.*, compounds derived from less complex basic alcohols than tropine and other acids than tropic). From this work, several antispasmodics emerged, which, although much less effective than atropine, achieved clinical recognition and served as the stimulus for the subsequent preparation of a large number of basic-alkyl esters of dialkyl, -alkylaryl- and diarylacetic acids and their structural variants.[1]

The antispasmodic activity of only a few basic alkyl esters of 2-thienyl substituted alkanoic acids has been investigated. Blicke and Tsao[2] found that a few esters of α-substituted 2-thienylacetic acids (I, R = C_6H_5, p-$C_6H_5C_6H_4$, 1-$C_{10}H_7$, 2-C_4H_3S) were effective anticholinergics. Blicke and Leonard[3] synthesized 2-diethylaminoethyl esters of α-



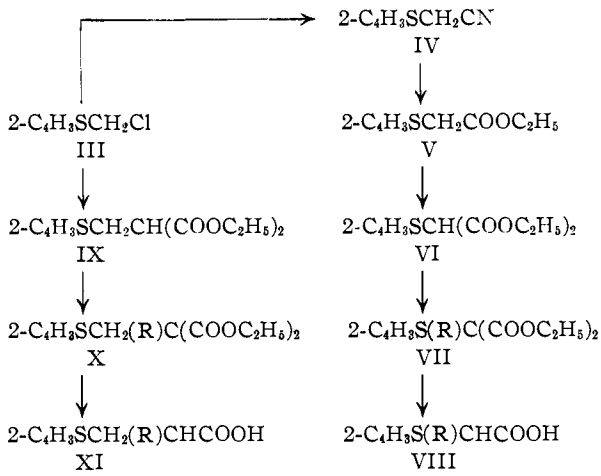
I



II

substituted β-(2-thienyl)-propionic acids [II, R = C_6H_5, C_6H_{11}, 2-C_4H_3S, $C_6H_5(CH_2)_n$, $C_6H_{11}(CH_2)_n$, 2-$C_4H_3S(CH_2)_n$]. Their data revealed that their preparations were less effective antispasmodics than the related 2-thienylacetic acid esters, an indication that a necessary structural feature for high antispasmodic activity is direct attachment of the 2-thienyl radical to the acetic acid residue.[4] This communication reports the synthesis, for pharmacological study, of tertiary aminoalkyl esters of hitherto undescribed α-substituted 2-thienylacetic acids of the general formula I, where R is an alkyl, alkenyl, cycloalkyl or 2-cycloalken-1-yl group, n is the integer 2 and R′ is ethyl and of α-substituted β-(2-thienyl)-propionic acids (Type II) where R is a 2-cycloalken-1-yl radical.

The synthesis of the intermediates needed for the preparation of esters of type I was accomplished as follows. Crude 2-thenyl chloride (III) was readily converted, when stirred and heated with an aqueous acetone solution of sodium cyanide to 2-thienylacetonitrile (IV) which gave on alcoholysis with 95% ethanol and sulfuric acid, ethyl 2-thienylacetate (V). The base-catalyzed carbethoxylation of



V with diethyl carbonate in the presence of sodium ethylate under forcing conditions yielded diethyl 2-thienylmalonate (VI). Alkylation of VI took place rapidly in absolute ethanol (method A) with 2-cycloalken-1-yl halides, more slowly with alkenyl halides. Diethyl carbonate was used as the reaction medium for the treatment of VI with alkyl halides (method B). Each reaction mixture was heated until a few drops, when quenched with water, reacted acid to phenolphthalein or produced a pink coloration no lighter than that given by the previous aliquot. The disubstituted malonic esters (VII, Table II) were saponified with aqueous alcoholic potassium hydroxide. Upon acidification, carbon dioxide was evolved and the disubstituted acetic acids (VIII, Table III) were isolated directly. To ensure complete decarboxylation of the intermediate malonic acids, the preparations were heated at 180° for one-half hour and distilled.

The requisite intermediates for the preparation

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(1) For review articles on antispasmodics see A. L. Raymond, *J. Am. Pharm. Assoc.*, **32**, 249 (1943); F. F. Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944); J. Levy, *J. Physiol. (Paris)*, **40**, 23 (1948); R. R. Burtner, "Medicinal Chemistry," Vol. I, C. M. Suter, John Wiley and Sons, Inc., New York, N. Y., 1951.

(2) F. F. Blicke and M. U. Tsao, THIS JOURNAL, **66**, 1645 (1944).

(3) F. F. Blicke and F. Leonard, *ibid.*, **68**, 1934 (1946).

(4) T. Wagner-Jauregg, H. Arnold and P. Born, *Ber.*, **72**, 1551 (1939), noted similar effects in the aromatic series of basic-alkyl esters,

TABLE I

2-DIETHYLAMINOETHYL ESTER HYDROCHLORIDES OF α-SUBSTITUTED 2-THIENYLACETIC AND β-(2-THIENYL)-PROPIONIC ACIDS

$2\text{-}C_4H_3S(CH_2)_n(R)CHCOOCH_2CH_2N(C_2H_5)_2\cdot HCl$

Cpd.	n	R	Recryst. Medium[a]	Yield,[b] %	M.p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Antispasmodic activity effective concn., γml./ Acetyl choline, 1γ/ml.	Barium chloride 0.20 mg./ml.	Histamine, 1γ/ml.	Toxicity, mg./kg. approx. mouse LD_{50} Intravenous	Subcutaneous
1	0	$CH_3CH_2CH_2$	A	67	95–96	$C_{16}H_{26}ClNO_2S$	4.38	4.25	11.09	11.30	1–2	1–5	5–30	50	750
2	0	$CH_3(CH_2)_2CH_2$	A	56	79–81[c]	$C_{16}H_{28}ClNO_2S$	4.20	4.24	10.62	10.68	1–5	3–10	3–10	50	750
3	0	$(CH_3)_2CHCH_2$	B	67	110–111	$C_{16}H_{28}ClNO_2S$	4.20	4.15	10.62	10.74	1–5	1	10–20	50	900
4	0	$CH_3(CH_2)_3CH_2$	C	73	[d]	$C_{17}H_{30}ClNO_2S$	4.02	4.15	10.19	10.36	0.5–1.0	1	5–10	60	750
5	0	$CH_3(CH_2)_4CH_2$	C	75	[d]	$C_{18}H_{32}ClNO_2S$	3.86	3.78	9.77	9.84	1–5	5–10	10–20	50	>1000
6	0	$CH_2=CHCH_2$	A	60	81–83	$C_{15}H_{24}ClNO_2S$	4.41	4.32	11.16	11.26	5–10	20–50	20	45	>1000
7	0	C_6H_5	A	47	122–123	$C_{17}H_{26}ClNO_2S$	4.05	3.93	10.25	10.22	0.1–1.0	1–5	5–10	65	1000
8	0	C_6H_{11}	E	45	143–144	$C_{18}H_{30}ClNO_2S$	3.89	3.85	9.85	9.70	0.5–1.0	10	5–10	50	1000
9	0	1-(2-C_5H_7)	E	48	130–132	$C_{17}H_{26}ClNO_2S$	4.07	3.97	10.31	10.34	0.2–0.5	0.5	5–10	44	750
10	1	1-(2-C_5H_7)	E	29	117–119	$C_{18}H_{28}ClNO_2S$	3.93	4.02	9.91	10.07	2–5	2–5	5–10		
11	0	1-(2-C_6H_9)	D	65	151–153	$C_{18}H_{28}ClNO_2S$	3.93	3.75	9.91	9.84	0.2–0.5	0.5–1.0	3	55	>1000
12	1	1-(2-C_6H_9)[e]	E	67	136–137	$C_{19}H_{30}ClNO_2S$	3.77	3.76	9.53	9.46	2	1–2	5		
		Trasentin									2–5	5–10	5–10	37.5	500–750

[a] Code: A, acetone–ether: B, benzene–ether; C, ethanol–ether: D, ethyl methyl ketone–ether; E, isopropyl alcohol–ether. [b] Yield after recrystallization. [c] Melting point taken in sealed tube. [d] Amorphous, hygroscopic, gummy solid; purified by repeated dissolution in ethanol and precipitation with ether. [e] Obtained from crude α-(2-cyclohexen-1-yl)-β-2-thienylpropionic acid. [f] Prophylactic dose needed to effect 50–75% inhibition of spasm of the isolated guinea pig ileum, induced by the test spasmogens.

of esters of type II were obtained in the following manner. Alkylation of diethyl malonate with crude 2-thenyl chloride gave diethyl 2-thenylmalonate (IX), the sodium enolate of which on metathesis with 2-cycloalken-1-yl halides yielded the esters, X. Saponification of the esters, X, using the conditions described for the saponification of VII, afforded the α-(2-cycloalken-1-yl)-β-2-thienylpropionic acids, XI.

On refluxing with 2-diethylaminoethyl chloride in isopropyl alcohol the acids of types VIII and XI were converted to ester hydrochlorides (I, II, Table I). In a number of instances the desired substance crystallized directly from the reaction mixture on cooling. Generally, it was necessary to concentrate the reaction mixture to a sirupy residue, and induce crystallization under ether in the cold or on standing in a desiccator over sulfuric acid and paraffin.

The antispasmodic activity and toxicity of our esters (Table I) were determined in the Department of Pharmacology of this Institute by Dr. R. J. Schachter, Miss M. Lewis and Mr. M. Chessin, to whom we are indebted for the data in Table I. It is evident on inspection of Table I, that in general the α-alkyl substituted 2-thienylacetates are less potent anticholinergics than the α-cycloalkyl and α-(2-cycloalken-1-yl)-2-thienylacetates which proved to be the most effective antispasmodics in the series. Replacement of the α-cycloalkyl or α-(2-cycloalken-1-yl)-group by the alkyl radical or separation of the 2-thienyl group from the rest of the molecule by a methylene group (substitution of the 2-thenyl for the 2-thienyl group) resulted in a significant decrease in activity in agreement with the findings reported by other investigators.[3,4]

Extensive pharmacological[5] and clinical[5] studies have established one of these compounds (No. 9), 2-diethylaminoethyl α-(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride[6] as a spasmolytic agent, which provides relief from spasm of the respiratory, gastro-intestinal and genito-urinary tracts.

(5) To be published elsewhere.

(6) Neotropine Hydrochloride Warner (U. S. Patent 2,561,385, July 24, 1951).

Experimental[7,8]

Ethyl 2-Thienylacetate.—2-Thienylacetonitrile[9] (1314 g., 10.7 moles) was mixed with a solution of 1150 ml. of concentrated sulfuric acid and 2590 ml. of 95% ethanol. The mixture was stirred and cautiously heated to reflux, where the reaction became very exothermic. After ten minutes the reaction subsided; the mixture was heated at reflux for six hours and let cool overnight. Water was added, the organic layer was separated and the aqueous layer was extracted twice with toluene. The combined organic layers were concentrated *in vacuo* and the product collected which boiled at 100–106° (6–7 mm.); yield 1232 g. (67.8%), $n^{20}D$ 1.5106; reported,[3] b.p. 119–121° (23 mm.).

The acetate was carbethoxylated under forcing conditions in the presence of commercial sodium methylate in 70–80% yield, by the procedure of Wallingford, *et al.*,[9] as modified by Blicke and Leonard,[3] to yield diethyl 2-thienylmalonate. Treatment of diethyl malonate with 2-thenyl chloride in the usual way gave diethyl 2-thenylmalonate.[3]

n-Propyl, *n*-butyl, *i*-butyl, *n*-amyl, *n*-hexyl, allyl bromide and methallyl chloride were purchased from the Eastman Kodak Co. Cyclopentyl and cyclohexyl bromide were prepared from the corresponding alcohols and phosphorus tribromide.[10] Cyclohexanol was obtained from Eastman Kodak Co. Cyclopentanol was obtained by hydrogenation of cyclopentanone over Raney nickel at 1500 lb. pressure and 100°[11]; the ketone was synthesized by dry distillation of adipic acid in the presence of barium hydroxide.[12] 2-Cyclohexen-1-yl bromide was prepared by the bromination of cyclohexene (generously supplied by the Dow Chemical Co.) with N-bromosuccinimide.[13] For the preparation of 2-cyclopenten-1-yl chloride, dicyclopentadiene (purchased, from Koppers Chemical Co.) was depolymerized by distillation over iron powder; a cyclopentadiene fraction was collected, b.p. 40–42° in a weighed quantity of dry toluene and

(7) Microanalyses were carried out by Mr. L. Dorfman in the Microanalytical Laboratory of this Institute.

(8) All melting points uncorrected.

(9) V. H. Wallingford, A. H. Homeyer and D. M. Jones, THIS JOURNAL, **63**, 2056 (1941).

(10) C. R. Noller and R. Adams, *ibid.*, **48**, 1084 (1926); G. R. Yohe and R. Adams, *ibid.*, **50**, 1505 (1928).

(11) H. Adkins and H. I. Cramer, *ibid.*, **52**, 4349 (1930).

(12) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 192.

(13) K. Ziegler, A. Späth, E. Schaaf, W. Schaunmann and E. Winkelman, *Ann.*, **551**, 80 (1942).

TABLE II

DISUBSTITUTED MALONIC ESTERS

$2\text{-}C_4C_3S(CH_2)_n(R)C(COOC_2H_5)_2$

Compound	n	R	Method[a]	Hours heated	Yield, %	B.p. °C.	Mm.	$n^{20}D$
1	0	$CH_3CH_2CH_2$	B	27	74	138–144	4.0	1.4928
2	0	$CH_3(CH_2)_2CH_2$	B	27	70	149–150	4.0	1.4909
3	0	$(CH_3)_2CHCH_2$	B	45	37	141–147	3.5	1.4918
4	0	$CH_3(CH_2)_3CH_2$	B	30	77	145–147	3.0	1.4897
5	0	$CH_3(CH_2)_4CH_2$	B	45	74	163–165	3.0	....
6	0	$CH_2{=}CHCH_2$	A	13	78	130–137	3.5	1.5026
7	0	$CH_2{=}C(CH_3)CH_2$	A	24	53	139–144	3.0	1.5041
8	0	C_5H_9	B	20	66	160–167	3.0	1.5128
9	0	C_6H_{11}	B	60	51	168–178[b]	4.0	...
10	0	1-(2-C_5H_7)	A	1¾	76	175–185	5.5	1.5200
11	1	1-(2-C_5H_7)	A	3	54	163–170	5.0	1.5142
12	0	1-(2-C_6H_9)	A	2	82	174–178	4.0	1.5239
13	1	1-(2-C_6H_9)	A	1.5	79	189–191	5.0	1.5181

[a] Method A: ethanol used as solvent. Method B: diethyl carbonate used as solvent. [b] M.p. 63–66°.

TABLE III

DISUBSTITUTED ACETIC ACIDS

$2\text{-}C_4H_3S(CH_2)_n(R)CHCOOH$

Compound	n	R	Yield, %	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	0	$CH_3CH_2CH_2$	68	137–140	4.0	58.76	58.86	6.57	6.72
2	0	$CH_3(CH_2)_2CH_2$	79	148–151	4.5	60.54	60.70	7.11	7.29
3	0	$(CH_3)_2CHCH_2$	67	142–144	4.0	60.54	60.68	7.11	6.66
4	0	$CH_3(CH_2)_3CH_2$	71	153–155	4.0	62.23	62.03	7.60	7.70
5	0	$CH_3(CH_2)_4CH_2$	82	168–172	5.0	63.68	63.97	8.02	8.05
6	0	$CH_2{=}CHCH_2$	64	136–140	5.0	59.31	59.56	5.54	5.57
7	0	$CH_2{=}C(CH_3)CH_2$	73	142–146	4.0	61.18	61.32	6.16	6.35
8	0	C_5H_9	82[a]	159–160	3.0	62.81	63.07	6.71	6.93
9	0	C_6H_{11}	70[b]	.....	...	...	...	..	..
10	0	1-(2-C_5H_7)	83[c]	161–166	3.0	63.43	63.35	5.81	5.91
11	1	1-(2-C_5H_7)	78	178–180	6.0	64.81	64.73	6.35	6.40
12	0	1-(2-C_6H_9)	73[d]	172–173	3.5	64.81	64.56	6.35	6.62
13	1	1-(2-C_6H_9)	79[e]	.....	...	...	...	..	..

[a] M.p. 73–75°. [b] M.p. 129–130°; Blicke and Tsao, ref. 2, reported m.p. 129–132°. [c] M.p. 60–65°. [d] M.p., 101–103°. [e] This compound decomposed on attempted distillation at 4 or 0.02 mm. It was therefore esterified without purification.

treated with gaseous hydrogen chloride at −20 to −15°.[14] When 80% of the theoretical equivalent of hydrogen chloride had been absorbed, the flow of gas was stopped, the percentage composition of 2-cyclopenten-1-yl chloride calculated and the solution used at once in the preparation of diethyl 2 cyclopenten-1-yl-2-thienyl malonate and diethyl 2-cyclopenten-1-yl-2-thenylmalonate.

Diethyl 2-Cyclopenten-1-yl-2-thienylmalonate.—Sodium (4.9 g., 0.213 g. atom) was dissolved in 150 ml. of absolute ethanol, the solution cooled to 50°, 38.7 g. (0.16 mole) of ethyl 2-thienylmalonate added at once, the mixture heated to reflux and then cooled to 0° in an ice–salt–bath. A toluene solution of 2-cyclopenten-1-yl chloride (39.7 g. containing 21.8 g., 0.213 mole of the reagent) was added dropwise during 20 minutes with constant stirring while the reagent and reaction mixture were kept at 0°. The mixture was stirred for one-half hour in the ice-bath, 4 hours at room temperature, let stand overnight and refluxed for 1.75 hours, at which time an aliquot gave an acid reaction with phenolphthalein. The following morning, alcohol was removed *in vacuo*, 50 ml. of water added, the organic layer separated and combined with the toluene extract of the aqueous phase. The combined organic layers were washed with water, the toluene removed *in vacuo* and the residual oil fractionated at 5.5 mm. Diethyl 2-cyclopenten-1-yl-2-thienylmalonate boiled from 175–185°: $n^{20}D$ 1.5200; yield 37.5 g. (76.4%).

The procedure utilized for the preparation of the 2-cyclohexen-1-yl and the alkenyl substituted malonates differed from that described above in that the reagent was added to the reaction mixture at temperatures of about 50° instead of at 0° and the mixtures immediately brought to reflux where heating and stirring was continued. Portions were tested periodically for alkalinity until the reactions appeared complete. All of the other disubstituted malonic esters were obtained in the same manner as diethyl cyclopentyl-2-thienylmalonate.

Diethyl Cyclopentyl-2-thienylmalonate.—A solution of 2.4 g. (0.105 g. atom) of sodium in 55 ml. of absolute ethanol was added dropwise to a refluxing solution of 24.2 g. (0.10 mole) of diethyl 2-thienylmalonate in 125 ml. of dry diethyl carbonate. The rate of addition of the sodium ethylate solution was equilibrated with the rate at which ethanol distilled out of the mixture in order to keep the alcohol concentration in the reaction mixture low. After removal of all of the alcohol (indicated by increase of distillate vapor temperature to 120°), 16.4 g. (0.11 mole) of cyclopentyl bromide was added and the mixture refluxed for 20 hours. Water was added to the cooled mixture, the layers separated and the aqueous layer extracted with toluene. Fractionation gave 20.3 g. (65.5%) of the disubstituted ester; b.p. 160–167° (3 mm.), $n^{20}D$ 1.5128.

The preparation of the acetic acids and their conversion to diethylaminoethyl esters is illustrated by the following procedures.

α-(2-Cyclopenten-1-yl)-2-thienylacetic Acid.—A mixture of 37.5 g. (0.122 mole) of diethyl 2-cyclopenten-1-yl-2-thienylmalonate, 27.4 g. (0.416 mole) of 85% potassium hydroxide, 27.4 ml. of water and 110 ml. of 95% ethanol was refluxed for 20 hours, cooled, alcohol removed by distillation *in vacuo*, the salt residue dissolved in water and extracted with ether. The alkaline solution was covered with

(14) G. A. Perkins and A. O. Cruz, THIS JOURNAL, 49, 518 (1927).

ether and acidified with concentrated hydrochloric acid. The vigorous evolution of gas on acidification indicated decarboxylation of the intermediate malonic acid. The organic layer was separated and the aqueous phase extracted with ether. The combined ether solutions were washed with water to neutrality and dried over anhydrous magnesium sulfate. Ether was removed, the residue heated at 180° for one-half hour (practically no evolution of gas) and distilled; yield, 21.0 g. (83.2%) of a yellow oil which boiled at 161–166° (3 mm.) and crystallized to a waxy solid melting at 60–65°.

2-Diethylaminoethyl α-(2-Cyclopenten-1-yl)-2-thienylacetate Hydrochloride.—A solution of 6.305 g. (0.0303 mole) of α-(2-cyclopenten-1-yl)-2-thienylacetic acid and 4.11 g. (0.0303 mole) of 2-diethylaminoethyl chloride in 80 ml. of absolute isopropyl alcohol was refluxed for 48 hours, cooled, filtered and evaporated to a sirup *in vacuo*.[15] Ether was added to the sirup and crystallization soon started. The mixture was placed in the refrigerator and after several hours the white crystalline mass was filtered off, washed with ether and dried *in vacuo;* yield 8.6 g. (82.7%), m.p. 120–125°. After two recrystallizations from an isopropyl alcohol–ether mixture the compound melted at 130–132°.

Acknowledgment.—The author is indebted to Mr. Leon Simet for technical assistance in the preparation of a number of the intermediates and basic-ester hydrochlorides described.

(15) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

NEW YORK 11, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. XXXI.[1] Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 4).[2] Saturated 7,11-Diones

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As exemplified in the allopregnane and 22-isoallospirostan series, steroidal Δ^8-11α-ol-7-ones can be isomerized smoothly with potassium *t*-butoxide to saturated 7,11-diones, which represent important intermediates in the synthesis of cortisone. The 7-keto group in 7,11-diones as well as in 7-one-11α-ols can be removed readily by conversion to the 7-cycloethylenemercaptol followed by desulfurization.

It was reported recently,[4,5] that performic acid oxidation of steroidal $\Delta^{7,9(11)}$-allodien-3β-ols leads to 9α,11α-oxido-7-ketones, which upon mild treatment with carbonate or alkali hydroxide[4,5] are isomerized smoothly to the corresponding Δ^8-11α-ol-7-ones (*e.g.*, I). Catalytic reduction of the 8,9-double bond followed by Wolff–Kishner reduction of the 7-keto function affords 11-oxygenated steroids, which are convertible to cortisone and related adrenal steroids.[6] Since Δ^8-11α-ol-7-ones (*e.g.*, I) are now readily available, it was of interest to study further reactions of this interesting ketol system with a view to develop alternate approaches to 11-oxygenated steroids.

By analogy to the conversion of Δ^4-cholesten-3-one-6β-ol to cholestane-3,6-dione,[7] Δ^8-allopregnene-3β,11α,20β-triol-7-one[4] (Ia) (ultraviolet absorpation maximum at 254 mμ) was refluxed with methanolic hydrochloric acid, but the resulting product exhibited maxima at 226 and 298 mμ; elementary analysis indicated the loss of one mole of water. These results coupled with the observation that the product formed a di- rather than triacetate and an oxime clearly confirm the structure of the substance as that of the dehydration product $\Delta^{8,11}$-allopregnadien-3β,20β-diol-7-one (IV). Similarly, attempts to prepare the enol acetate of the triacetate Ib followed by alkaline saponification resulted in dehydration and isolation of the dienone IV. While ordinary alkaline saponification conditions suffice to accomplish the isomerization of the Δ^4-3-one-6β-ol system to the corresponding saturated 3,6-dione,[7,8] the 6α-ol isomer is much more resistant[8] to such treatment. This is also true of the Δ^8-11α-ol-7-ones (I, VII), since they are, in fact, products of the alkaline treatment of epoxyketones.[4,5] It is significant that the hydrogen atom which is difficult to remove by base is polar in both the 6α- and 11α-hydroxyl compounds. It was found, however, that if the Δ^8-allopregnene-3β,11α,20β-triol (Ia) was refluxed with potassium *t*-butoxide in anhydrous *t*-butyl alcohol, there was obtained in over 90% yield an isomeric substance, which exhibited no selective absorption in the ultraviolet and whose infrared spectrum showed only the presence of saturated carbonyl and free hydroxyl groups. The subsequent transformations of this substance established its constitution as the desired isomerization product allopregnane-3β,20β-diol-7,11-dione (IIa). Thus it formed a diacetate (IIb), a monoöxime (IIc) and a monocycloethylenemercaptol (IId), which upon desulfurization with Raney nickel afforded allopregnane-3β,20β-diol-11-one diacetate (IIe). The structure of the desulfurization product IIe was proved by saponification to the 3,20-diol-11-one (IIf), which still showed an infrared carbonyl band, and by oxidation to the known allopregnane-3,11,-20-trione (VI).[4,9] This reaction sequence (*t*-butoxide isomerization, mercaptol formation and desulfuri-

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