oil separated. The mixture was stirred cold (ice-bath) for one hour and then for 2 hours at room temperature. After adding just enough water to dissolve the solid salts that had formed, the two liquid layers were separated. The aqueous layer was extracted well with ether and the ether washings were added to the original oil. This ether solution was washed well with saturated sodium bisulfite solution, water, saturated brine and then dried over anhydrous magnesium sulfate. After filtering, the ether solvent was removed under reduced pressure with very gentle external heating and the residual oil dried to constant weight. The yield of crude colorless product was 270 g. This could not be distilled and thus was used directly in the following preparations without further purification.

N-Methyl-γ-cyano-γ-valerolactam.—(Procedure A) A solution of 34.2 g. (0.2 mole) of ethyl γ-cyano-γ-hydroxyvalerate and 20 cc. (0.5 mole) of methylamine in 50 cc. of 12A alcohol was heated in a bomb for 8 hours at 125°. The solvent was removed on a steam-bath under reduced pressure and the residual red oil was distilled to give 23.3 g. (85%) of a faint yellow oil, b.p. 102–103° at 1.7 mm., $n^{25}D$ 1.4793. This was redistilled to give 19.8 g. of product, b.p. 107–109° at 2.8 mm., $n^{25}D$ 1.4785.

Anal.[17] Calcd. for $C_7H_{10}N_2O$: N, 20.28. Found: N, 20.28.

N-Butyl-γ-cyano-γ-valerolactam.—(Procedure B) A solution of 6.00 g. (0.035 mole) of ethyl γ-cyano-γ-hydroxyvalerate and 2.90 g. (0.04 mole) of *n*-butylamine was allowed to stand about 16 hours at room temperature. The two layers which had formed were separated and the organic layer was dissolved in 50 cc. of 12A alcohol and the solution was refluxed 15 hours. After standing overnight at room temperature the solvent was removed under reduced pressure. The residual oil was dissolved in ether and the ether solution washed with 5% hydrochloric acid, water, saturated brine, clarified with Darco and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed to give 4.20 g. of a crude oil. This was distilled to give 2.28 g. (31.6%) of a colorless oil, b.p. 97–98.5° at 0.5 mm., $n^{26}D$ 1.4642.

Anal.[17] Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.78; H, 8.70; N, 15.13.

N-(β-Cyanoethyl)-γ-cyano-γ-valerolactam.—A mixture of 5.60 g. (0.045 mole) of γ-cyano-γ-valerolactam, 2.50 g. (0.047 mole) of acrylonitrile and one pellet of sodium hydroxide was warmed gently on a steam-bath with occasional shaking until liquefaction had taken place. Heating was then continued for an additional 30 minutes. The resulting sirup was cooled and scratched until it solidified. Recrystallization from 3A alcohol gave 2.97 g. of colorless needles, m.p. 78–80°. From the mother liquor was isolated an additional 0.53 g. of product, m.p. 72–80°, making a total yield of 43.9%. A further recrystallization from 3A alcohol gave colorless prisms, m.p. 75–77°.

Anal.[17] Calcd. for $C_9H_{11}N_3O$: N, 23.71. Found: N, 23.87.

Ethyl γ-Cyano-γ-dimethylaminovalerate.—A solution of 60.0 g. (0.575 mole) of sodium bisulfite and 72.0 g. (0.5 mole) of ethyl levulinate in 150 cc. of water was stirred 2 hours at room temperature. To this was added 135 g. (0.75 mole) of a 25% solution of dimethylamine and the resulting solution stirred 2 hours at room temperature. After the addition of 28.2 g. (0.575 mole) of sodium cyanide the resulting mixture was stirred two hours at room temperature. Sufficient water was added to dissolve the solids that had formed and the layers were separated. After extracting the aqueous phase three times with ether the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. After filtering, the ether was removed under reduced pressure and the residual oil was distilled to give 10.1 g. (14%) of recovered ethyl levulinate, 3.8 g. of an intermediate fraction and 37.2 g. (37.8%) of the desired product, b.p. 130–132° at 15 mm., $n^{26}D$ 1.4462.

Anal.[17] Calcd. for $C_{10}H_{18}N_2O_2$: N, 14.13. Found: N, 14.02.

NORTH CHICAGO, ILLINOIS
PHILADELPHIA, PENNSYLVANIA

(17) Analysis by E. F. Shelberg and staff, Abbott Laboratories.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Compounds Related to Chloromycetin.[1] 1-Biaryl-2-dichloroacetamido-1,3-propanediols

BY MILDRED C. REBSTOCK AND CHARLOTTE D. STRATTON

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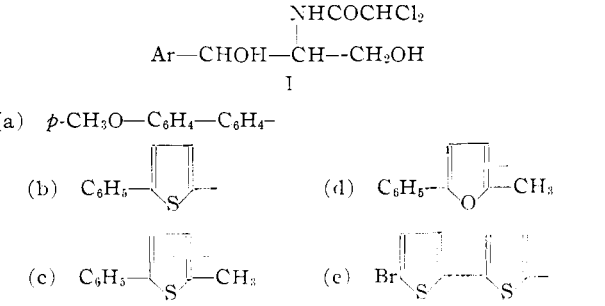
Several compounds related to DL-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol have been synthesized. These include analogs having thiophene, 2-methylthiophene and 2-methylfuran groups substituted for the phenyl attached to the side chain. The preparations of 1-(4'-methoxybiphenylyl)- and 1-(2-bromobithienyl)-2-dichloroacetamido-1,3-propanediol are also given.

The demonstration of the marked antibacterial activity of D-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol and of the corresponding racemic *p*-methylbiphenylyl and *p*-bromobiphenylyl derivatives[2] has motivated the preparation of a number of related compounds Ia, Ib, Ic, Id and Ie. These include the *p*-methoxybiphenylyl analog, as well as compounds having either or both of the phenyl rings replaced with heterocyclic aromatic rings. The syntheses of 2-dichloroacetamido-1-(2-naphthyl)-1,3-propanediol and its 4-nitro-1-naphthyl analog have previously been described by Long and Troutman[3] while Feitelson, *et al.*,[4] have prepared the 2-quinolyl compounds. In a recent publication Morris and Smith[5] outlined the synthesis of 1-(*p*-thiazoylphenyl)-2-dichloroacetamido-1,3-propanediol.



Starting materials for the synthesis of these compounds were the corresponding biaryls: 2-phenyl-

(1) Parke, Davis & Company registered trademark for chloramphenicol.

(2) M. C. Rebstock, C. D. Stratton and L. L. Bambas, THIS JOURNAL, **77**, 24 (1955).

(3) L. M. Long and H. D. Troutman, *ibid.*, **73**, 542 (1951).

(4) B. N. Feitelson, J. T. Gunner, R. J. Moualim, V. Petrow, O. Stephenson and S. W. F. Underhill, *J. Pharm. Pharmacol.*, **3**, 149 (1951).

(5) D. S. Morris and S. D. Smith, *J. Chem. Soc.*, 1680 (1954).

thiophene,[6] 2-methyl-5-phenylthiophene,[7] 2-methyl-5-phenylfuran,[8] 2,2′-bithiophene[9] and *p*-methoxybiphenyl. A modification of the versatile method described by Long and Troutman[10] for the synthesis of Chloromycetin and other substituted 2-phenyl-2-dichloroacetamido-1,3-propanediols was employed in the preparation of the biaryl related compounds (I). The biaryls were first converted to α-bromomethyl ketones which readily gave hexamethylenetetramine salts. Acid hydrolysis of the complexes yielded biaryl-α-aminomethyl ketone hydrohalide salts which were converted without further purification to the more stable biaryl-α-dichloroacetamidomethyl ketone intermediates. Hydroxymethylation of these products followed by the Meerwein–Verley–Ponndorf reduction of the carbonyl groups gave the desired racemic 1-biaryl-2-dichloroacetamido-1,3-propanediols.

The α-bromomethyl ketones were prepared when possible in a one-step Friedel–Crafts reaction in which the biaryl and bromoacetyl bromide were condensed with the aid of aluminum chloride. Under these conditions 2,2′-bithiophene and 2-methyl-5-phenylfuran reaction mixtures decomposed. Methyl ketone derivatives of these biaryls were prepared by condensation with acetic anhydride in the presence of a catalytic quantity of phosphoric acid in the former case, while aluminum chloride was used in the latter example. The use of phosphoric acid in the preparation of 2-acetothienone has been described by Hartough and Kosak.[11]

When one equivalent of bromine was added to a methanol solution of 2,2′-(5-acetyl)-bithiophene, ring bromination occurred. Addition of a second equivalent of bromine gave 2,2′-(5-bromo-5′-α-bromoacetyl)-bithiophene. Since 1-(4′-bromobiphenylyl)-2-dichloroacetamido-1,3-propanediol is nearly as active an antibacterial agent as the unsubstituted biphenyl compound, no attempt was made to remove the ring halogen; the 2,2′-(5-bromo)-bithiophene group being considered analogous to the 4′-bromobiphenylyl radical.

Bromination of the acetyl derivative of 2-methyl-5-phenylfuran gave an oily product which was immediately converted to the crystalline hexamethylenetetramine complex. The structure was verified by characterization of the dichloroacetamido derivative of the α-aminoacetyl-2-methyl-5-phenylfuran intermediate and subsequent products in the synthesis.

A comparison of the ultraviolet absorption spectra[12] of the various biaryl-α-dichloroacetamido-β-hydroxypropionyl compounds and their Meerwein–Verley–Ponndorf reduction products was useful in determining the position of substitution in certain of the Friedel–Crafts syntheses. The ultraviolet absorption data for certain of the key products and model compounds have been summarized in Table I. The 2-(dichloroacetamido)-1,3-propanediol-substituted 2-phenylthiophene has an absorption maximum at λ292 mμ, ε16,200. The absorption spectrum of this compound is nearly identical with that of 2-methyl-5-phenylthiophene, and the observed absorption is essentially due to the phenylthiophene nucleus. The α-dichloroacetamido-β-hydroxypropionyl derivative of 2-phenylthiophene has absorption maxima at λ334 mμ, ε22,000 and λ231 mμ ε10,400. This spectrum is characteristic of the 2-phenylthiophene system substituted with an acyl group in the 5-position of the thiophene ring. The assignment follows from the method of preparation of the key intermediate, 5-bromoacetyl-2-phenylthiophene. When bromoacetyl bromide and phenylthiophene are condensed under the usual conditions of the Friedel–Crafts reaction, the latter compound is the main product of the reaction.

In 2-methyl-5-phenylthiophene both α-positions of the heterocyclic ring systems are substituted, and acylation must occur in the β-position of the thiophene ring or in the benzene ring. It was hoped that phenyl substitution would occur since this intermediate would be useful in the preparation of the analog of 1-(4′-methylbiphenylyl)-2-dichloroacetamido-1,3-propanediol having a 2-methylthiophene radical substituted for the terminal *p*-tolyl group. With this compound for study together with the phenylthiophene analog previously described, a comparison could be made of the effect of substituting a thiophene nucleus for each of the phenyl groups of the biphenyl compound. In the event substitution occurred in the β-position of the thiophene ring, the product would be useful in the synthesis of one of the β-analogs of 1-(5-phenyl-2-methylthienyl)-2-dichloroacetamido-1,3-propanediol.

To determine in which ring substitution occurred, a comparison of the ultraviolet absorption spectra of the α-dichloroacetamido-β-hydroxypropionyl-2-methyl-5-phenylthiophene and acetyl-2-methyl-5-*p*-tolylthiophene was made. The latter compound was prepared by condensing 2-methyl-5-*p*-tolylthiophene with acetyl chloride under conditions similar to those used in the preparation of the 2-methyl-5-phenylthiophene bromoacetyl intermediate. The marked similarity of the ultraviolet absorption spectra of these compounds indicated that acylation occurred in the same position in both molecules (see Table I). Since the *para* position was blocked in the model *p*-tolylthiophene compound, substitution at this position in 2-methyl-5-phenylthiophene is excluded. *Meta* or *ortho* substitution in the phenyl nucleus is theoretically unlikely, and only the *beta* positions of the thiophene nucleus remain for consideration. It has not been rigorously established which of the two β-positions is involved.

Although model compounds were not available for a similar study in the 2-methyl-5-phenylfuran series, the ultraviolet absorption curves of the α-dichloroacetamido-β-hydroxypropionyl biaryl and the corresponding Meerwein–Verley–Ponndorf reduction product were analogous to the absorption curves of the 2-methyl-5-phenylthiophene derivatives and warrant similar conclusions concerning

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(7) C. Paal, *Ber.*, **18**, 369 (1885).

(8) C. Paal, *ibid.*, **17**, 66, 2757 (1884).

(9) W. Steinkopf and J. Roch, *Ann.*, **482**, 260 (1930).

(10) L. M. Long and H. D. Troutman, THIS JOURNAL, **71**, 2469 (1949).

(11) H. D. Hartough and A. L. Kosak, *ibid.*, **69**, 3093 (1948).

(12) We are indebted to Dr. J. M. Vandenbelt and Miss Carola Henrich and co-workers of these laboratories for the ultraviolet absorption studies presented in this paper.

TABLE I

Compound	λmax or λ*Inflection, mμ	ε × 10⁻³	λmax, mμ	ε × 10⁻³
2-Methyl-5-phenylthiophene	225*	6.2	291	16.2
1-(5-Phenyl-2-thienyl)-2-(dichloroacetamido)-1,3-propanediol	229*	7.3	292	16.2
2-[α-(Dichloroacetamido)-β-hydroxypropionyl]-5-phenylthiophene	231	10.4	334	22.0
1-[5-(5-Bromo-2-thienyl)-2-thienyl]-2-(dichloroacetamido)-1,3-propanediol	250*	5.5	320	17.0
2-[α-(Dichloroacetamido)-β-hydroxypropionyl]-5-(5-bromo-2-thienyl)-thiophene	255	6.9	362	23.8
2-Methyl-5-*p*-tolylthiophene	226*	6.8	292	17.4
Ar-Acetyl-2-methyl-5-*p*-tolylthiophene	252	29.9	287	15.1
1-(2-Methyl-5-phenyl-3(or 4)-thienyl)-2-(dichloroacetamido)-1,3-propanediol	228*	8.0	295	15.1
3(or 4)-[α-(Dichloroacetamido)-β-hydroxypropionyl]-2-methyl-5-phenylthiophene	254	30.9	287	13.5
1-(2-Methyl-5-phenyl-3(or 4)-furyl)-2-(dichloroacetamido)-1,3-propanediol	223*	9.4	288	19.3
3(or 4)-[α-(Dichloroacetamido)-β-hydroxypropionyl]-2-methyl-5-phenylfuran	218	27.4	280	24.0

TABLE II[14]

1-BIARYL-2-DICHLOROACETAMIDO-1,3-PROPANEDIOLS AND INTERMEDIATES USED IN PREPARING THESE COMPOUNDS

CH_2OH

ArCHOH—CH—$NHCOCHCl_2$ (I)

Ar	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-Phenyl-2-thienyl	138–139	$C_{15}H_{15}Cl_2NO_3S$	50.01	50.19	4.20	4.31	3.89	4.07
2-Methyl-5-phenyl-3(or 4)-thienyl(a)	108–109	$C_{16}H_{17}Cl_2NO_3S$	51.34	51.35	4.58	4.92	3.75	4.00
2-Methyl-5-phenyl-3(or 4)-furyl	69–70	$C_{16}H_{17}Cl_2NO_4 \cdot H_2O$	51.08	51.43	5.18	4.86	3.72	3.77
2-(5-Bromo-2-thienyl)-5-thiophene	113–114	$C_{13}H_{12}BrCl_2NO_3S$	35.07	35.30	2.72	3.09	3.15	3.08
4′-Methoxy-4-biphenylyl	143.5–144	$C_{18}H_{19}Cl_2NO_4$	56.26	56.38	4.98	4.97	3.65	3.70
ArCO—$CH_2NHCOCHCl_2$ (II)								
5-Phenyl-2-thienyl	179–180	$C_{14}H_{11}Cl_2NO_2S$	51.23	51.16	3.38	3.43	4.27	4.22
2-Methyl-5-phenyl-3(or 4)-thienyl(a)	147–148	$C_{15}H_{13}Cl_2NO_2S$	52.64	52.67	3.83	4.11	4.09	4.03
2-Methyl-5-phenyl-3(or 4)-furyl(b)	135.5–136	$C_{15}H_{13}Cl_2NO_3$	55.23	55.18	4.02	4.55	4.29	4.42
2-(5-Bromo-2-thienyl)-5-thiophene	188–190	$C_{12}H_8BrCl_2NO_2S$	34.88	35.04	1.95	2.22	3.39	3.31
4′-Methoxy-4-biphenylyl(c)	181–182	$C_{17}H_{15}Cl_2NO_3$	57.91	57.98	4.29	4.55	3.98	4.08
CH_2OH								
ArCO—CHNHCOCHCl₂ (III)								
5-Phenyl-2-thienyl(a)	165–166	$C_{15}H_{13}Cl_2NO_3S$	50.29	50.48	3.66	3.30	3.91	3.84
2-Methyl-5-phenyl-3(or 4)-thienyl(b)	133.5–134.5	$C_{16}H_{15}Cl_2NO_3S$	51.62	51.44	4.06	4.41	3.76	3.68
2-Methyl-5-phenyl-3(or 4)-furyl(c)	187–188	$C_{16}H_{15}Cl_2NO_4$	53.95	54.11	4.24	4.41	3.93	3.84
2-(5-Bromo-2-thienyl)-5-thiophene(d)	168–169	$C_{13}H_{10}BrCl_2NO_3S_2$	35.23	35.34	2.28	2.38	3.16	3.12
4′-Methoxy-4-biphenylyl	178.5–179.5	$C_{18}H_{17}Cl_2NO_4$	56.56	56.26	4.48	4.43	3.67	3.53

the course of substitution in the Friedel–Crafts reaction. The assignment of the acyl group to the furan ring is further supported by a synthesis of 2,5-diphenyl-3-acetylfuran which is described by Lutz and Rowlett.[13]

The ultraviolet absorption spectra data of the α-dichloroacetamido-β-hydroxypropionyl derivatives and Meerwein–Verley–Ponndorf reduction products of the 2-bromobithiophene compounds are also summarized in Table I. It is of interest to compare these curves with the absorption curves of 1-(5-phenyl-2-thienyl)-2-dichloroacetamido-1,3-propanediol and its ketone intermediate. The shifting of the absorption of the carbonyl substituted biaryl toward the longer wave lengths in each case is of course indicative of the change in resonance characteristics due to the substitution of the carbonyl function in the α-position of the thiophene nucleus.

(13) R. A. Lutz and R. J. Rowlett, THIS JOURNAL, **70**, 1359 (1948).

(14) Ethylene dichloride was used in the recrystallization of analytical samples with the following exceptions: (Ia and IIa) ethanol, (IIb) ethylene dichloride, ethanol, (IIc) ethanol, ethylene dichloride, ethyl acetate, (IIIa) ethylene dichloride, ethyl acetate, (IIIb and IIIe) ethylene dichloride, ethanol, (IIIc) ethyl acetate, ethanol and (IIId) ethanol, ethylene dichloride.

The compounds described were tested for antibacterial, antiviral and antifungal activity. The 4′-methoxybiphenylyl analog had *in vitro* antibacterial activity similar to that of DL-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol.[2] In *in vitro* antibacterial tests, 1-(5-phenyl-2-thienyl)-2-dichloroacetamido-1,3-propanediol showed slight activity against four out of twenty-eight strains of bacteria. The 2-bromothienyl analog, Ie, was slightly active against six organisms in the above group, while the 5-methylfurylphenyl, Id, and 5-methylthienylphenyl analogs, Ic, were inactive against a group of six strains of bacteria which are sensitive to Chloromycetin.

Although the above Chloromycetin related compounds can exist in two racemic forms, only a single racemate was obtained as a pure crystalline entity from the Meerwein–Verley–Ponndorf reduction of the ketone intermediates. Since the *p*-methoxybiphenylyl compound, Ia, had activity comparable to that of the 1-(4′-methylbiphenylyl)-2-dichloroacetamido-1,3-propanediol, it is thought that this compound has the *threo* configuration. The *p*-methylbiphenylyl *erythro* compound is without ap-

appreciable antibacterial activity. The present evidence is insufficient for a definite assignment of configuration to the heterocyclic biaryl derivatives. It can, however, be pointed out that in all the examples known to date in which a ketone intermediate of the α-dichloroacetamido-β-hydroxy substituted propiophenone type was reduced using Meerwein conditions, the *threo* isomer was obtained as the main product. For this reason it is probable that certain of the mixed biaryl derivatives have the *threo* configuration, particularly in those cases where the compounds exhibited antibacterial activity. In instances where the yields of reduced product were low, the possibility that the material isolated represented the *erythro* isomer was considered, although in each case the poor yield could also be attributed to a fundamental instability of the ketone intermediates as well as of the final product of the reduction.

Experimental

5-Phenyl-2-α-bromoacetothienone.—To 86 g. of 2-phenylthiophene[6] and 120 g. of bromoacetyl bromide in 250 ml. of carbon disulfide was added 66 g. of aluminum chloride in portions during 45 min. The reaction mixture was refluxed for 2.5 hr. longer, then quenched on a mixture of ice and 50 ml. of concentrated HCl. The product was extracted into *ca.* 800 ml. of ethyl acetate. The ethyl acetate was washed three times with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from ligroin. To remove color the product was dissolved in hot ethanol, treated with Norite® and then crystallized by chilling to yield 25 g. of crystalline material which melted at 110–115°. An analytical sample was prepared by a final recrystallization from ethanol and melted at 115–116°.

Anal. Calcd. for $C_{12}H_9BrO_5S$: C, 51.26; H, 3.23. Found: C, 51.20; H, 3.41.

α-Bromoacetyl-2-methyl-5-phenylthiophene.—Treatment of 35 g. of 2-methyl-5-phenylthiophene[7] with bromoacetyl bromide under the above conditions gave a crystalline product in 12 g. yield which analyzed for the presence of two bromomethyl ketone side chains, m.p. 138–139°. The desired monobromoacetyl derivative of 2-methyl-5-phenylthiophene was not isolated as a pure entity. When the 45 g. of gummy residue remaining from evaporation of the mother liquors of the above product was treated with hexamethylenetetramine in chloroform solution, a crystalline complex was obtained. This substance underwent acid hydrolysis in the usual manner and the amino ketone hydrochloride product was characterized by conversion to the dichloroacetamide. Recrystallization of the crude amide from ethanol gave 10.7 g. of essentially pure α-dichloroacetamidoacetyl-2-methyl-5-phenylthiophene, m.p. 146–148°.

Acetyl-2-methyl-5-*p*-tolylphenylthiophene.—2-Methyl-5-*p*-tolylthiophene was prepared in the same manner as 2-methyl-5-phenylthiophene. The synthesis of the latter compound by heating levulinylbenzene with phosphorus pentasulfide was first described by Paal.[7] In the present synthesis, the corresponding levulinyltoluene was employed to give a product melting at 44.5–45° after three recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{12}H_{12}S$: C, 76.54; H, 6.42. Found: C, 76.17; H, 6.48.

Acetyl chloride was condensed with the above biaryl in carbon disulfide solution with the aid of aluminum chloride. The details of the synthesis are similar to those described in the preparation of 5-phenyl-2-bromoacetothienone. The analytical sample was recrystallized from isopropyl alcohol to a melting point of 103.5–104.5°.

Anal. Calcd. for $C_{14}H_{14}O_5S$: C, 73.01; H, 6.13. Found: C, 73.31; H, 6.01.

5-(5′-Bromo-2′-thienyl)-2-α-bromoacetothienone.—5-(2′-Thienyl)-2-acetothienone was prepared by heating 73 g. of 2,2′-bithiophene with 49.4 g. of acetic anhydride containing 1 ml. of 85% phosphoric acid for 3 hours on the steam-bath. The reaction mixture was then diluted with 500 ml. of water and extracted with 1 l. of ethyl acetate. The ethyl acetate extract was shaken with saturated sodium bicarbonate solution until neutral, then washed with water and dried and evaporated. A solution of the orange residue in 450 ml. of benzene when kept for 20 hours in the refrigerator yielded a mixture of 17.0 g. of mono and diacetylation products. Separation of the latter compound was achieved by redissolving in 250 ml. of benzene and refrigerating for 3 hours. A yield of 4.4 g. of product (m.p. 228–230°)[15] was filtered off. Refrigeration of the filtrate overnight gave 0.5 g. of additional material. The mother liquor was combined with the mother liquor from which the 17 g. had originally separated and evaporated. The residue was dissolved in absolute ethanol, boiled with norite and filtered. A total of 39 g. of crude 5-(2′-thienyl)-2-acetothienone was obtained (m.p. 108–111°).

Bromination was carried out in two steps. To 37 g. of the above monoacetyl product was added 30 g. of bromine dropwise during 10 min. The temperature was kept at 12° by means of a cooling bath. After the bromine had been added, the reaction mixture was allowed to return to room temperature and stirred for 1.5 hr. longer. The yellow crystalline product was filtered off and recrystallized from 500 ml. of ethylene dichloride to give 30.5 g. (m.p. 170–172°) of 5-(5′-bromo-2-thienyl)-2-acetothienone.

Anal. Calcd. for $C_{10}H_7BrOS_2$: C, 41.81; H, 2.46. Found: C, 42.02; H, 2.77.

The presence of the bromine in the ring rather than on the methyl group adjacent to the carbonyl was indicated by failure of the compound to react with hexamethylenetetramine. The above product was suspended in 500 ml. of chloroform and stirred at 22° for 30 min. while an additional equivalent of bromine was added dropwise. The bromination mixture was stirred for 30 min. longer, then the chloroform was removed at reduced pressure. The residue was crystallized from absolute ethanol to give 34 g. of product melting at 108–112°. A single recrystallization from ethyl acetate yielded 33.0 g. (m.p. 125–127°) of essentially pure 5-(5′-bromo-2′-thienyl)-2α-bromoacetothienone. An analytical sample was prepared by recrystallization from a benzene–low boiling petroleum ether mixture (m.p. 128–129°).

Anal. Calcd. for $C_{10}H_6Br_2OS_2$: C, 32.81; H, 1.65. Found: C, 32.42; H, 1.96.

Bromoacetyl-2-methyl-5-phenylfuran.—Acetyl 2-methyl-5-phenylfuran was prepared by treating a mixture of 51 g. of 2-methyl-5-phenylfuran and 30 g. of acetic anhydride in carbon disulfide solution with 51 g. of aluminum chloride. The last material was added portionwise as described in a preceding example. The product was isolated as usual and distilled at 115–118° (0.5 mm.) to give 32.7 g. of the methyl ketone derivative. One equivalent of bromine was added dropwise to a chloroform solution of the ketone at 36–40° during 30 min. After stirring at room temperature for 30 min. longer, the chloroform was evaporated and the oily residue taken into ethyl acetate, washed to neutrality with saturated aqueous sodium bicarbonate solution, then finally washed with water and dried and evaporated. The dark brown oil obtained at this point appeared to be unstable and was therefore immediately converted to the hexamethylenetetramine complex by dissolving in 100 ml. of chloroform and stirring with 20 g. of hexamethylenetetramine overnight. The product was filtered on a buchner funnel and washed with ether to remove most of the color (yield 28.7 g.).

α-Dichloroacetamidomethylbiaryl Ketone Intermediates (II).—Hexamethylenetetramine complexes of the α-bromomethyl-ketones were prepared in chloroform solution in the usual manner.[10] The products were isolated by filtration and hydrolyzed without purification with mixtures of concentrated hydrochloric acid and ethanol. Of the aminoketones prepared in this manner, only the 5-phenyl-2-α-aminoacetothienone hydrochloride was recrystallized for analysis.

Anal. Calcd. for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.77; N, 5.52. Found: C, 56.60; H, 4.80; N, 5.52.

To conserve material the crude amino ketone hydrochlorides were suspended in dimethylformamide solution and sufficient dichloroacetyl chloride was added in portions to react with the amine present. The presence of ammonium chloride in such preparations did not interfere with the re-

(15) W. Steinkopf and H. J. V. Petersdorff, *Ann.*, **543**, 119 (1940).

action and since the product was isolated by dilution with water, the salt was effectively separated. When the product separated as a gum, it was taken into ethyl acetate. The ethyl acetate extract was washed with water and saturated sodium bicarbonate solution, then dried and evaporated. The products were recrystallized for analysis as indicated in Table II.

Hydroxymethylation of α-Dichloroacetamidomethyl Biaryl Ketone Intermediates (III).—The α-dichloroacetamidomethylaryl ketones described above were treated with two to three equivalents of 36–38% aqueous formaldehyde in 95% ethanol in the presence of a catalytic quantity of sodium bicarbonate. The reaction was allowed to proceed at 40° for 2 to 5 hours as described in other publications.[2,10]

Treatment of a 9.0-g. portion of 2-phenyl-5-dichloroacetamidoacetothienone in the above manner gave 980 mg. of a dihydroxymethylated compound in addition to the desired product. Similar dihydroxymethylation products have been described as by-products in the hydroxymethylation of α-dichloroacetamido-*p*-nitroacetophenone[16] and the corresponding *p*-methoxyacetophenone analog.[17] The dihydroxymethylated by-product in this case melted at 209–210° after two recrystallizations from ethanol. Hydroxyl absorption in the infrared also ruled out the possibility of a bis analog, another type of by-product which is sometimes obtained in such reactions.

Anal. Calcd. for $C_{16}H_{15}Cl_2NO_4S$: C, 49.49; H, 3.89; N, 3.61. Found: C, 49.70; H, 3.94; N, 3.41.

(16) F. Sorm, J. Gut, M. Suchy and D. Reichl, *Collection Czechoslov. Chem. Communs.*, 501 (1951); J. Sicher, J. Farkas and F. Sorm, *Chem. Listy* **46**, 483 (1952).

(17) M. C. Rebstock and E. L. Pfeiffer, THIS JOURNAL, **74**, 3207 (1952).

The monohydroxymethylation derivative II was the main product of the reaction. In certain of the above biaryl derivatives, the analytical differences between dihydroxymethylation, monohydroxymethylation and bis products do not satisfactorily distinguish between the three possibilities. For better identification, acetyl derivatives were prepared using either the ketone or the product obtained in the Meerwein-Verley-Ponndorf reduction of the ketone. Acetylations were carried out in pyridine in the presence of excess acetic anhydride. The products were isolated by removing the pyridine, excess acetic anhydride, and pyridine acetate on the vacuum pump and recrystallizing from a suitable solvent. 5-(α-Dichloroacetamido-β-acetoxypropionyl)-2-(5-bromo-2-thienyl)-thiophene was recrystallized for analysis from ethylene dichloride, then ethyl acetate, and finally ethanol (m.p. 168–169°).

Anal. Calcd. for $C_{15}H_{12}BrCl_2NO_4S_2$: C, 37.13; H, 2.49; N, 2.88. Found: C, 36.83; H, 2.76; N, 2.75.

1-(2-Methyl-5-phenylthienyl)-2-dichloroacetamido-1,3-propanediol diacetate was recrystallized for analysis from ethylene dichloride–low boiling petroleum ether mixture and finally from ethanol (m.p. 119–120°).

Anal. Calcd. for $C_{20}H_{21}Cl_2NO_5S$: C, 52.41; H, 4.62; N, 3.06; $COCH_3$, 18.8. Found: C, 52.56; H, 4.81; N, 3.04; $COCH_3$, 20.0.

Preparation of 1-Biaryl-2-dichloroacetamido-1,3-propanediols (I).—The β-hydroxy-α-dichloroacetamidopropionylbiaryl intermediates III were reduced in every case using Meerwein–Verley–Ponndorf conditions. The reaction was carried out and the products isolated in essentially the manner described in preceding publications.[2,3,10]

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXIV. The Hydrochloric Acid Catalyzed Equilibration of 22ξ,25D- and 22ξ-25L-Spirostanes[2]

BY MONROE E. WALL, SAMUEL SEROTA AND LEE P. WITNAUER

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Prolonged heating of sarsasapogenin with ethanolic hydrochloric acid gives a mixture containing sarsasapogenin, smilagenin and the corresponding Δ^2- or Δ^3-desoxy analogs. On studying the reaction with desoxysarsasapogenin and desoxysmilagenin, it was found that an equilibration occurs in both cases in which formation of the more stable smilagenin isomer is favored. The significance of these results in relation to methods for acidic hydrolysis of saponins are discussed.

Recently there have appeared a number of papers dealing with the stereochemistry of the spiroketal side chain[3a–i] Although the stereochemistry of carbon 20[3c,e] and the configuration of carbon 25[3a,b] seem well established, the question of the configuration of carbon 22 and the related matter of the conformation of the methyl group attached to carbon 25 are still unsettled (*cf.* references 3a, b, d, e, h and i).

In an attempt to obtain further information on the nature of the spiroketal side chain, we decided to study the effect of hydrochloric acid on sapogenins with 22ξ,25D- and 22ξ,25L-configurations.[4,5] Marker and Rohrmann[6] reported that sarsasapogenin (25L) was converted to smilagenin (25D) on prolonged heating with ethanolic hydrochloric acid. Other workers starting with the 25L-sapogenins neotigogenin[3f] and markogenin[7] reported similar conversions to the analogous 25D-sapogenins, tigogenin and samogenin.

When sarsaspogenin (I) 22ξ,25L-spirostan-3β-ol, was refluxed with hydrochloric acid under Marker's conditions[6] and the reaction product carefully chromatographed, surprisingly *four* sapogenins were obtained. In order of elution we found 2?-22ξ,25D-spirostene (II), 2?-22ξ,25L-spirostene (III), smilagenin (22ξ,25D-spirostan-3β-ol (IV) and sarsasapogenin (I). Of these II and IV were major con-

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(2) Paper XXIII, C. R. Eddy, M. A. Barnes, C. S. Fenske, accepted by *Anal. Chem.*

(3) (a) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **75**, 4871 (1953); (b) V. H. T. James, *Chem. and Ind.*, 1388 (1953); (c) M. E. Wall, C. R. Eddy, and S. Serota, THIS JOURNAL, **76**, 2849 (1954); (d) M. E. Wall and S. Serota, *ibid.*, **76**, 2850 (1954); (e) M. E. Wall, S. Serota and C. R. Eddy, *ibid.*, **77**, 1230 (1955); (f) R. K. Callow and V. H. T. James, *Chem. and Ind.*, 691 (1954); (g) D. H. W. Dickson, *et al.*, *ibid.*, 692 (1954); (h) D. A. H. Taylor, *ibid.*, 1066 (1954); (i) J. B. Ziegler, W. E. Rosen and A. C. Shabica, THIS JOURNAL, **76**, 3865 (1954).

(4) As a result of the researches of Scheer, *et al.*,[3a] and of James,[3b] smilagenin and other 22 "iso" sapogenins have the D configuration at carbon 25, whereas sarsasapogenin and presumably other 22 "normal" sapogenins have the L configration.

(5) G. Mueller and B. Riegel have proposed the use of 25D and 25L to denote configuration at carbon 25. We wish to thank Dr. Mueller for giving us this information prior to publication.

(6) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 846 (1939).

(7) M. E. Wall, *et al.*, *ibid.*, **75**, 4437 (1953).