stirring for 20 min. at 9–15°, the mixture was cooled to 3–6° and treated, dropwise, with 20 ml. (20.8 g., 0.21 mole) of acetic anhydride. The resulting mobile suspension was stirred for 6 hr. at room temperature, allowed to stand overnight, and finally heated under reflux for 4 hr. Hydrogen chloride gas (8 g.) was then bubbled into the cooled reaction mixture at 5–10° to liberate the N-acetyl-L-cysteine from its sodium salt. The thick suspension was made mobile by the addition of THF and filtered to remove sodium chloride. The product was isolated by carefully concentrating the filtrate under reduced pressure at 40–50° and crystallizing the residual oil from 35 ml. of warm (45–50°) water: yield, 26.3 g. (80.6%) of white solid in two crops; m.p. 109–110°; pK_a = 3.2; $[\alpha]^{25}D$ +21.64° (*c* 5, dilute NaOH, pH 7), +4.07° (*c* 2.7, water); lit.[2] $[\alpha]^{21}_{546}$ +6.3° (*c* 2.7, water).

Anal. Calcd. for $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; SH, 20.2. Found: C, 36.78; H, 5.72; N, 8.54; SH, 19.9.

Yields of 65–77% were obtained when sodium hydroxide, ammonium hydroxide, or tribasic sodium phosphate was used as the acid acceptor in place of sodium acetate. The substitution of other reaction solvents for THF gave the following yields: methanol, 70%; 2-propanol, 78%; and water, 66%. Acetylation of L-cysteine base under anhydrous conditions in methanol, using 1 equiv. of sodium methoxide as the acid acceptor, gave a 67% yield.

When the above reaction was carried out with 2 equiv. of acetic anhydride, N,S-diacetyl-L-cysteine[10] was obtained in 34% yield.

N-Succinoyl-L-cysteine.—The use of 20 g. (0.2 mole) of succinic anhydride gave an oily product which was slurried with 150 ml. of anhydrous ether to yield 41.6 g. of crude solid, m.p. 131–132°. Two recrystallizations from water gave 9.7 g. (22%) of white solid, m.p. 141–142°, $[\alpha]^{25}D$ +4.5° (*c* 3, water).

Anal. Calcd. for $C_7H_{11}NO_5S$: C, 38.00; H, 5.01; N, 6.33; SH, 14.9. Found: C, 38.38; H, 5.08; N, 6.03; SH, 14.6.

N-Propionyl-L-cysteine.[8]—Propionic anhydride (26.4 g., 0.202 mole) was added slowly at 0–5° to a stirred suspension (under nitrogen) of 35.2 g. (0.2 mole) of L-cysteine hydrochloride monohydrate, 38.4 g. (0.4 mole) of sodium propionate, and 98 ml. of 80% aqueous THF. The reaction mixture was treated as described above, except that liberation of product was achieved by the slow addition of concentrated hydrochloric acid (18 ml.): yield, 21.7 g. (61%); m.p. 89–90°; $[\alpha]^{25}D$ +24.3° (*c* 5, dilute NaOH, pH 7).

Anal. Calcd. for $C_6H_{11}NO_3S$: C, 40.67; H, 6.26; N, 7.90; SH, 18.6. Found: C, 40.77; H, 6.24; N, 7.69; SH, 18.6.

(10) A. Neuberger, *Biochem. J.*, **32**, 1452 1938).

An Unusual Formation of a Benzothiophene Derivative

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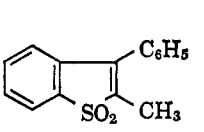
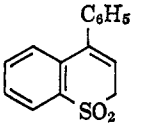
The cycloisomerization of allylbenzenes to hydrindenes is a well-known reaction; it is catalyzed by acids. In an attempt to use propenyl- instead of the isomeric allylbenzenes, the reaction of 1,1-diphenylpropene ($C_{15}H_{14}$) with sulfuric acid has been studied. It gave a well-crystallized product of the formula $C_{15}H_{12}O_2S$, which obviously arises from the reaction $C_{15}H_{14} + H_2SO_4 \rightarrow C_{15}H_{12}O_2S + 2H_2O$. The new compound contains a double bond, as hydrogenation gives the equally well-defined $C_{15}H_{14}O_2S$ and the infrared spectrum (KBr pellet) indicated the presence of a sulfone group; the peaks at 1300, 1176, and 1152 cm.$^{-1}$ correspond to the known infrared spectra of sulfones.[1] The ultraviolet spectrum shows a strong bathochromic shift in comparison with the starting material. It resembles somewhat that of indene: $C_{15}H_{12}O_2S$, 228 mμ (log ε 4.54), 254 (3.79, infl.), and 312 (3.38) (in ethanol); 1,1-diphenylpropene,[2] 235 mμ (log ε 3.87) and 248 (3.94) (in ethanol); indene,[3] 249 mμ (log ε 3.97) 279 (2.72), 285 (2.48), and 290 (2.26) (in ethanol).

These data establish for the compound $C_{15}H_{12}SO_2$ one of two possible formulas (I or II).

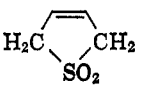


I

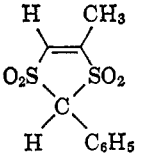


II

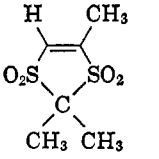
The choice between them has been based on the n.m.r. spectrum which consists of a very sharp signal at τ = 8.0 p.p.m. and a broad multiplet between τ = 2.35 and 3.1 p.p.m. The ratio of the two maxima is 2–3:9–10. Obviously, there is no vinyl hydrogen in the molecule (which would give a signal at about τ = 4.0 p.p.m.), and the comparison with the following examples indicates that the substance contains a methyl and not a methylene next to the sulfone group. The signal at



τ 6.26[4]



doublet at τ 7.62, 7.66[5]



doublet at τ 7.66, 7.70[5]

τ = 8 p.p.m. corresponds to the methyl, that at τ = 2.35–3.1 p.p.m. to the aromatic hydrogen atoms. Formula I of 2-methyl-3-phenyl-benzothiophene 1,1-dioxide is thus correct.

The n.m.r. spectrum of the dihydro derivative confirms these conclusions. It is composed of a doublet at τ = 9.15 p.p.m. (3 methyl protons), a quartet at τ = 6.62 p.p.m. (one proton at C-2), a doublet at τ = 5.91 p.p.m. (one proton at C-3), and a multiplet at τ = 2.3–3.4 p.p.m. (representing the nine protons of the aromatic rings).

Compound I is equally well obtained from ethyldiphenylcarbinol as from 1,1-diphenylpropylene, and substitution products appear to behave analogously. Thus, 1,1-di(*p*-chlorophenyl)propylene gives a product $C_{15}H_{10}Cl_2O_2S$ which has an infrared spectrum very similar to that of I and is thus very probably 5-chloro-3-(*p*-chlorophenyl)-2-methylbenzothiophene 1,1-dioxide.

This curious reaction recalls somewhat the observation of Kharasch[6] that styrene reacts with bisulfite in the presence of oxygen to give $C_6H_5 \cdot CHOH \cdot CH_2 \cdot$-

Kresze, U. Uhlich, E. Ropte, and B. Schrader, *Z. Anal. Chem.*, **197**, 283 (1963); R. J. Gaul and W. J. Fremuth, *J. Org. Chem.*, **26**, 5103 (1961); G. W. Michel and H. R. Snyder, *ibid.*, **27**, 2034 (1962).

(2) C. Djerassi, M. Shamma, and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958); *cf.* J. Cymermam-Craig and R. J. Harrsson, *Australian J. Chem.*, **8**, 378 (1955), and N. Campbell and D. A. Crombie, *Chem. Ind.* (London), 600 (1959).

(3) M. Donbrow, *J. Chem. Soc.*, 1963 (1959).

(4) "NMR Spectra Catalog," Vol. II, Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 406.

(5) R. J. S. Beer, D. Harris, and D. J. Reyall, *Tetrahedron Letters*, 1531 (1964).

(6) M. S. Kharasch, R. T. E. Schenck, and F. R. Mayo, *J. Am. Chem. Soc.*, **61**, 3092 (1939). We are grateful to one of the referees for drawing our attention to this paper.

SO_3H and $C_6H_5 \cdot CH{=}CH \cdot SO_3H$. In our case, the analogous initial product would lose two molecules of water instead of one. It would seem not impossible that the cycloisomerization of allylbenzenes proceeds *via* similar addition products.

Experimental

1,1-Diphenylpropanol has been prepared from propiophenone and phenylmagnesium bromide,[7] m.p. 95° (from ethanol) (lit.[8] m.p. 94–95°). The dehydration was carried out according to Klages[8]; **1-1,diphenylpropylene** boiled at 149° (11 mm.).

2-Methyl-3-phenylbenzothiophene 1,1-Dioxide (I). A.—A mixture of 2 g. of 1,1-diphenylpropylene and 20 ml. of concentrated sulfuric acid was kept at room temperature for 1 week and poured into cold water. The solid was filtered and recrystallized from petroleum ether (b.p. 90–100°), yield 0.5 g., m.p. 114°. In all experiments, the balance of material consisted of water-soluble, sulfonated products which were not further investigated.

B.—A mixture of 10 g. of 1,1-diphenylpropanol and 50 ml. of concentrated sulfuric acid was kept at room temperature for 7 days and the brownish green solution was poured into water. The precipitate (7 g.) was recrystallized from petroleum ether (b.p. 70–90°) and formed needles, m.p. 114°.

Anal. Calcd. for $C_{15}H_{12}O_2S$: C, 70.3; H, 4.7; S, 12.5; mol. wt., 256. Found: C, 70.4; H, 5.0; S, 12.4; mol. wt., 248 (Rast method).

2-Methyl-3-phenyl-2,3-dihydrobenzothiophene 1,1-Dioxide.—The foregoing substance (4 g.) in 120 ml. of boiling propanol was treated for 4 hr. with hydrogen in the presence of palladium on barium sulfate (2 g.). On cooling, the filtered solution deposited the dihydro derivative of I, which was recrystallized from propyl alcohol and melted at 169–170°. The yield was almost quantitative.

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.7; H, 5.4. Found: C, 69.8; H, 5.4.

5-Chloro-3-(*p*-chlorophenyl)-2-methylbenzothiophene 1,1-Dioxide.—The reaction of *p*-chlorophenylmagnesium bromide (3 moles) and ethyl propionate (1 mole) gave, after the usual work-up, a product of sharp boiling point (178° at 2 mm.) which, however, according to the analysis consisted of a mixture of 1,1-di(*p*-chlorophenyl)propylene and 1,1-di(*p*-chlorophenyl)propanol; it was used directly for the next step.

Anal. Calcd. for $C_{15}H_{12}Cl_2$: C, 68.4; H, 4.6. Calcd. for $C_{15}H_{14}Cl_2O$: C, 64.0; H, 5.0. Found: C, 65.6; H, 4.5.

A mixture of 1 g. of the product and 10 ml. of concentrated sulfuric acid was kept at room temperature for 4 days and poured into ice–water. The solid product was filtered and recrystallized from ethanol. Thus, 440 mg. (yield 40%) of a colorless product, m.p. 236°, was obtained.

Anal. Calcd. for $C_{15}H_{10}Cl_2O_2S$: C, 55.4; H, 3.1; Cl, 21.8; S, 9.9. Found: C, 55.6; H, 3.1; Cl, 21.8; S, 10.2.

The n.m.r. spectra were measured in deuteriobenzene at 60 Mc., using tetramethylsilane as internal standard.

(7) C. Hell and H. Bauer, *Ber.*, **37**, 230 (1904).

(8) A. Klages, *ibid.*, **35**, 2646 (1902); A. Klages and S. Heilmann, *ibid.*, **37**, 1447 (1904).

16-Keto 19-Norsteroids.[1] Long-Range Conformational Effects

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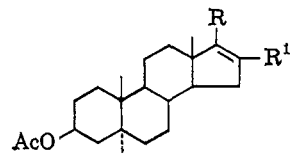
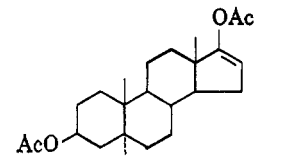
The presence of long-range conformational effects in steroids has been a well-recognized phenomenon.[2] These effects are reflected in rate differences of reactions at specific sites due to structural changes in distant parts of the molecule. This Note reports on an even more drastic effect on reactions in ring D due to structure alterations in ring A. An attempt is also made to define the cause for this effect.

Both 17-oxo-5α-androstan-3β-ol and 17-oxo-estra-1,3,5(10)-trien-3-ol give the respective enol diacetates Ia and II in essentially quantitative yield under mild conditions.[3] However, the corresponding 16-keto compounds give widely divergent results. 16-Oxo-5α-androstan-3β-ol yields the enol diacetate Ib although in consistently poorer yield than the corresponding 17-keto compound[4]; in contrast, the 16-keto estrogen derivative IV failed to yield any enol acetate under various conditions.[5,5a] Clearly, this change in the ease of enolization of the 16-ketone must be occasioned by the changes in ring A structure, *i.e.*, aromatic unsaturation and lack of the C-19 methyl group. In an effort to isolate the cause, the effect of only one of these changes on the enolization of the 16-ketone was of interest. The 16-keto-19-norandrostane structure provides a suitable substrate since it lacks



Ia, R = CH_3COO; R^1 = H

b, R = H; R^1 = CH_3COO



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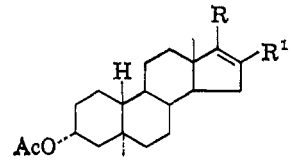
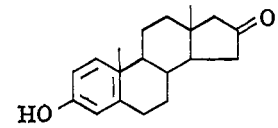
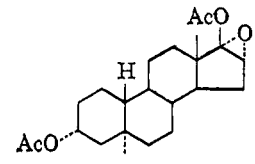


IIIa, R = CH_3COO; R^1 = H

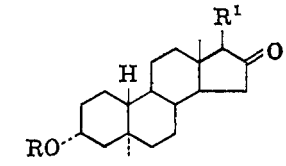
b, R = H; R^1 = CH_3COO



IV



V



VIa, R = H; R^1 = OH

b, R = CH_3CO; R^1 = CH_3COO

c, R = CH_3CO; R^1 = H

d, R = R^1 = H

(1) This research was supported by a grant from the American Cancer Society and Grant CA 03704 from the National Cancer Institute.

(2) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).

(3) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

(4) J. Fajkos and J. Joska, *Chem. Ind.* (London), 872 (1960); J. Fishman, *ibid.*, 1078 (1961).

(5) J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960).

(5a) NOTE ADDED IN PROOF.—The preparation of the enol diacetate from 16-oxoestra-1,3,5(10)-trien-3-ol has just been reported: J. R. Rhone and M. N. Huffman, *Tetrahedron Letters.*, **No. 19**, 1395 (1965). The authors have informed us that the reaction is successful only in the presence of *anhydrous* *p*-toluenesulfonic acid as catalyst, and they confirm our findings that the reaction fails when *p*-toluenesulfonic acid monohydrate is used. Since the estrone IV and androstane 16-keto VIa derivatives yield enol diacetates in the presence of the monohydrate a significant difference in the enol stability must exist and the views offered in this Note require no amendment.

(6) D. K. Fukushima and S. Dobriner, *J. Org. Chem.*, **26**, 3022 (1961).