$$\overset{-}{RCH=N-N-tosyl}$$

Solvent	2,4-Cl₂C₆H₃	m-O₂NC₆H₄	C₆H₅	o-HOC₆H₄	p-(C₂H₅)₂NC₆H₄
	λ, mμ (log ϵ^a)			λ, mμ (log ϵ)	
HCON(CH₃)₂	368.5 (4.13)	351 (4.18)	345 (4.23)	342 (4.34)	337 (4.40)
CH₃CN	355 (4.28)	342 (4.30)	334 (4.15)	337 (4.37)	332 (4.42)
C₂H₅OH	334.5 (4.25)	321 (4.25)	313 (4.12)	325 (4.23)	325 (4.53)
CH₃OH	329 (4.29)	315 (4.25)	310.5 (4.26)	322 (4.23)	325 (4.41)
H₂O	313 (4.27)	297 (4.29)	303 (4.24)	322 (4.19)	325 (4.36)

^{a} Estimated by extrapolation to zero time.

group (e.g., $^-O_2N=C_6H_4=CH-N=N$-tosyl) contribute greatly to the excited state. The increased resonance stabilization in these latter forms is manifested by the large energy shift in changing from a protic to a nonprotic solvent. On the other hand, the effect of an electron-donating substituent such as the diethylamino group would be to favor resonance forms with high electron density at the nitrogen atom (e.g., $Et_2N-C_6H_4-CH=N-N^-$-tosyl). The contribution of resonance forms in which the negative charge is delocalized ($Et_2N-^-C_6H_3=CH-N=N$-tosyl) will be small even in nonhydrogen-bonding solvents, hence leading to only small transition energy differences between protic and nonprotic solvents. The total energy changes observed range from 16.6 kcal./mole for the p-nitro compound to 3.6 kcal./mole for the p-diethylamino compound. These energies are for the most part much larger than those observed for the energy of the hydrogen bond, which is on the order of 2 to 10 kcal./mole.[15] Therefore, the total energy shifts should be related to the energy gained through stabilization of the ground state plus the energy gained through the destabilization of the excited state in the hydrogen-bonding solvents.[16]

The effect of solvents manifests itself also in the rate at which the tosylhydrazones decompose. At room temperature the p-nitrobenzaldehyde derivative anion decomposed in aprotic dissociating solvents approximately 15 times as fast as in the hydrogen-bonding solvents, confirming the spectroscopically observed stabilization of the ground state by the latter solvents. The half-life of a 10^{-4} M solution was about 2 min. in DMF vs. about 30 min. in ethanol. In the cases of the 2,4-dichlorobenzaldehyde, m-nitrobenzaldehyde, and benzaldehyde derivatives, the rates of decomposition in nonprotic solvents were also faster than in protic solvents. The rates were, however, considerably slower than for the p-nitro compound in the expected order: 2,4-dichloro- > m-nitro- > benzaldehyde. These decomposition reactions were followed spectroscopically by observing the rate of disappearance of the anion bands. The o-hydroxy and p-diethylamino tosylhydrazone anions appeared to be stable at room temperature indefinitely. In the case of the p-nitro compound, p-nitrophenyldiazomethane could be isolated as a stable solid.

(15) L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell University Press, Ithaca, N. Y., 1960, p. 449.
(16) This situation appears to be similar to the n → π* carbonyl transition discussed by Kosower.[14] We wish to thank the referee for pointing this out to us.

Conversion of Methyl 17β-Acetoxy-5-oxo-3,5-seco-4-norestran-3-oate to $\Delta^{9(11)}$-Testosterone[1]

JULIUS A. VIDA AND MARCEL GUT

Worcester Foundation for Experimental Biology,
Shrewsbury, Massachusetts

A review of recent total syntheses shows that most of them, especially the most efficient ones, led to 19-norsteroids. A recently published total synthesis[2] commanded our attention because an intermediate seemed to be a good starting material to produce analogs possessing a 19-methyl group. We had a further interest in this problem because of our desire to introduce a radioactive label at C-19.[3]

The key intermediate in our synthesis of adrenosterone, 17β-hydroxy-5-oxo-3,5-seco-4-norestr-9-en-3-oic acid (I),[4] had already been obtained by total synthesis. As an alternative, a partial synthesis makes use of the known methyl 17β-acetoxy-5-oxo-3,5-seco-4-norestran-3-oate[5] which was brominated selectively at C-10 with N-bromosuccinimide and the resulting crude bromide was dehydrobrominated with lithium chloride in N,N-dimethylformamide to give 17β-hydroxy-5-oxo-3,5-seco-4-norestr-9-en-3-oic acid (I).

There remained the introduction of the angular methyl group at C-10, already mentioned without disclosure of details, in a review article by Velluz, et al.,[2a] in a closely related case. To the solution of I in N,N-dimethylformamide sodium hydride was added, followed by the addition of a catalytic amount of methanol and then by a large excess of methyl iodide. The absence of any α,β-unsaturated ketone in the isolated crude product demonstrates that the methylation had taken place at C-10, thus making it unnecessary to block C-6.[6] Simultaneous methylation of the

(1) Supported, in part, by National Institutes of Health Grant H-5266. Presented, in part, before the Division of Organic Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, Abstracts of Papers, p. 40S.
(2) (a) L. Velluz, G. Nomine, and J. Mathieu, Angew. Chem., 72, 725 (1960); (b) L. Velluz, G. Nomine, G. Amiard, V. Torelli, and J. Cerede, Compt. rend., 257, 3086 (1963); (c) British Patent 914,738 (Jan. 2, 1963).
(3) S. Rakhit and M. Gut, J. Am. Chem. Soc., 86, 1432 (1964).
(4) L. J. Chinn and H. L. Dryden, Jr., J. Org. Chem., 26, 3904 (1961).
(5) Free acid described by J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, J. Am. Chem. Soc., 78, 5662 (1956).
(6) Cf. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, ibid., 74, 4223 (1952); L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, ibid., 78, 4111 (1956).
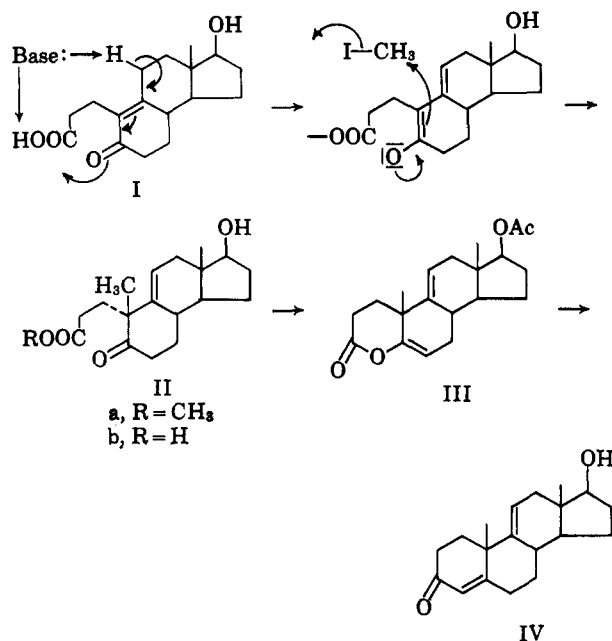
C-3 carboxyl gave rise to the methyl ester. This keto ester IIa was hydrolyzed to its acid IIb and the latter was converted to the enol lactone III. A Grignard reaction on the lactone, followed by hydrolysis and cyclization in the usual manner[7] produced the desired $\Delta^{9(11)}$-testosterone (IV). Its conversion to adrenosterone has already been described.[2a,8]

Experimental[9]

17β-Hydroxy-5-oxo-3,5-seco-4-norestr-9-en-3-oic Acid (I).— Methyl 17β-acetoxy-5-oxo-3,5-seco-4-norestran-3-oate (7.250 g., 20.7 mmoles) was dissolved in a mixture of 350 ml. of carbon tetrachloride and 100 ml. of n-pentane. To this solution 3.91 g. (22 mmoles) of N-bromosuccinimide was added and the mixture was refluxed and illuminated by a 500-w. photospot lamp for 30 min. The mixture was cooled, the precipitated succinimide (1.942 g.) was filtered off, and the solution was evaporated at room temperature to dryness under reduced pressure. The residue was dissolved in 70 ml. of N,N-dimethylformamide, 3.4 g. of lithium chloride was added, and the solution was kept at 100° for 4 hr. The solution was diluted with ether, and ice was added. The aqueous phase was separated and the ether layer was washed with water, 2 N hydrochloric acid, water, saturated sodium bicarbonate solution, and water. The ether solution was dried and evaporated to afford an oil (6.2 g.). This was chromatographed on 300 g. of silica gel (Davison 923), whereby the eluates with benzene–ethyl acetate (9.5:0.5) gave 1.9 g. of methyl 17β-acetoxy-5-oxo-3,5-seco-4-norestran-3-oate (starting material). Further elution with the same solvent mixture gave 504 mg. of a compound which appeared to be a mixture. Elution with a 9:1 mixture of benzene–ethyl acetate afforded 3.46 g. (73.5% conversion, 65% yield) of methyl 17β-acetoxy-5-oxo-3,5-seco-4-norestr-9-en-3-oate which appeared uniform on a thin layer chromatogram.

The methyl ester was dissolved in 50 ml. of methyl alcohol, and 5 ml. of 40% sodium hydroxide solution was added. The solution was refluxed under nitrogen for 2 hr. and then concentrated under reduced pressure at room temperature. Acidifi-

cation with 2 N hydrochloric acid and crystallization of the resulting precipitate from aqueous ethanol afforded 2.60 g. (58.5%) of 17β-hydroxy-5-oxo-3,5-seco-4-norestr-9-en-3-oic acid: m.p. 195–198°; λ_{max}^{MeOH} 248 mμ (ε 14,600); ν_{max} 3472, 1745, 1712, 1626, and 1600 cm.$^{-1}$.

17β-Hydroxy-5-oxo-3,5-seco-4-norandrost-9(11)-en-3-oic Acid (IIb).— To the solution of 1 g. of 17β-hydroxy-5-oxo-3,5-seco-4-norestr-9-en-3-oic acid in 100 ml. of distilled N,N-dimethylformamide 1 g. of sodium hydride (51% suspension in mineral oil) was added. The reaction flask was heated under nitrogen at 100° for 1 hr., then cooled to 0°, and 2 drops of methyl alcohol was added. After stirring the reaction mixture for 15 min., 5 ml. of methyl iodide was added and the stirring was continued at room temperature for 2 hr. Ether was added and then ice and saturated sodium chloride solution. The product was extracted with ether; the ether solution was dried and evaporated. The crude reaction mixture was chromatographed on 100 g. of silica gel (Davison 923), whereby the eluates with benzene–ethyl acetate (7:3) gave 940 mg. (85%) of compound IIa which appeared uniform on a thin layer chromatogram. A 6:4 mixture of benzene–ethyl acetate eluted an additional 95 mg. of a compound which was not further identified.

The methyl ester II was dissolved in 25 ml. of methyl alcohol and 2 ml. of 15% sodium hydroxide solution was added. The solution was refluxed under nitrogen for 1 hr., 2 ml. of a 15% sodium hydroxide solution was added, and heating was continued for another hour. The solution was concentrated under reduced pressure at room temperature to a small volume, water was added, and, after acidification to pH 4 with 2 N hydrochloric acid, the compound was extracted with ether. The ethereal solution was dried and evaporated to dryness. The residual oil was crystallized from ether–hexane, and the analytical sample was prepared by crystallization from aqueous ethyl alcohol to give colorless plates: m.p. 167.5–168°; $[\alpha]^{21}$D +48° (c 1.4, methanol); infrared absorption maxima, ν_{max} 3440, 3200–3100, 2900–2800, 1703, and 1633 cm.$^{-1}$; no ultraviolet absorption between 220–280 mμ; n.m.r. spectrum, τ 3.47 (COOH), 4.38 (11-H), 6.12 (17α-H), 8.75 (19-CH₃), 9.18 (18-CH₃); τ (in C₅D₅N) 4.32 (11-H), 6.05 (17α-H), 8.73 (19-CH₃), 9.00 (19-CH₃).

Anal. Calcd. for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.25; H, 8.55.

5-Hydroxy-17β-acetoxy-3,5-seco-4-norandrosta-5,9(11)-dien-3-oic Acid 3,5-Lactone (III).— To the solution of 1.0 g. of 17β-hydroxy-5-oxo-3,5-seco-4-norestr-9(11)-en-3-oic acid in 20 ml. of acetic anhydride was added 200 mg. of fused sodium acetate, and the mixture was heated at reflux under nitrogen for 2 hr. Then the solvent was evaporated to dryness under reduced pressure and ice was added. After acidification with 2 N hydrochloric acid, the compound was extracted with ether, and the solution was dried over sodium sulfate and evaporated to dryness. The oily residue was chromatographed on 100 g. of silica gel (Davison, grade 923), whereby a mixture of benzene–ethyl acetate 9:1 eluted 850 mg. (78%) of enol lactone acetate. Recrystallization from ethanol gave colorless plates: m.p. 118–120°; $[\alpha]^{21}$D −86° (c 1.7, methanol); infrared absorption maxima, ν_{max} 1750, 1727, 1683, 1643, 1262, 1248 cm.$^{-1}$; no selective ultraviolet absorption above 220 mμ; n.m.r. spectrum, τ 4.46 and 4.59 (6-H and 11-H), 5.29, 7.29, 7.41, 7.95 (17α-H), 8.73 (19-CH₃), 9.21 (18-CH₃).

Anal. Calcd. for C₂₀H₂₆O₄: C, 72.70; H, 7.93. Found: C, 72.86; H, 7.77.

Δ⁹⁽¹¹⁾-Testosterone (IV).— A 10% excess of a standardized methylmagnesium iodide solution was added dropwise over a period of 1 hr. to a stirred solution of 265 mg. of enol lactone acetate III in 50 ml. of benzene–ether (1:1) which was kept at ca. −15° with exclusion of air for an additional hour. Then cold dilute hydrochloric acid was added to the reaction mixture, and the compound was extracted with ether. The organic layer was washed with water, dried, and evaporated to dryness under reduced pressure. A solution of 660 mg. of potassium hydroxide in 1 ml. of water and 20 ml. of methyl alcohol was added to the residue, and the mixture was heated at reflux under nitrogen for 2 hr. The solvent evaporated under reduced pressure at room temperature to a small volume, saturated sodium bicarbonate solution was added, and the compound was extracted with ethyl acetate. The organic layer was washed with water and chromatographed on 50 g. of silica gel. A mixture of benzene–ethyl acetate (9:1) eluted 8 mg. of a compound showing an infrared absorption at 1700 cm.$^{-1}$. Further elution with benzene–ethyl acetate (8:2) gave 13 mg. of a mixture, exhibiting in the infrared

(7) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950); G. I. Fujimoto, *ibid.*, **73**, 1856 (1951).

(8) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953); R. H. Lenhard and S. Bernstein, *ibid.*, **77**, 6665 (1955).

(9) Melting points were determined on a Fisher-Johns apparatus and are corrected. The ultraviolet absorption spectra were determined in methanol on a Cary Model 14 recording spectrophotometer and the infrared spectra in a potassium bromide pellet (Infracord). The elemental analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, 77, N. Y. The n.m.r. spectra were obtained in deuteriochloroform solution with a Varian Model V-4300B spectrometer, using tetramethylsilane as an internal standard.

spectrum a saturated ketone and an enone absorption, and benzene–ethyl acetate (7:3) eluted 114 mg. (50%) of $\Delta^{9(11)}$-testosterone. Crystallization from aqueous ethyl alcohol and methylene chloride–hexane afforded colorless crystals, m.p. 153–154°, identical in all respects with an authentic sample.[10]

(10) The authors are indebted to the Upjohn Co., Kalamazoo, Mich., for kindly supplying an authentic sample of $\Delta^{9(11)}$-testosterone.

Studies Concerning the Infrared Spectra of Some Substituted Benzofuran Derivatives

W. W. Epstein, W. J. Horton, and C. T. Lin

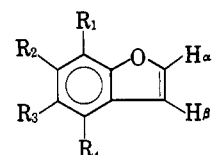Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Although a number of studies of the infrared spectra of furan-type compounds have been reported,[1-8] these investigations with one exception[1] have been limited to monosubstituted or simple polysubstituted derivatives. Three groups of these workers have made some generalizations concerning characterizing bands. Katritzky and Lagowski[2] found nine bands to be common and identified with the furan nucleus in 24 2-monosubstituted furans. Kubota[3] after considering the spectra of 43 furano compounds has suggested three bands as being characteristic of the furan group. On the basis of 20 compounds most of which were 2,3-disubstituted furan derivatives of complex furanoquinoline alkaloids and furanocoumarins, Briggs and Colebrook[1] proposed that seven bands characterized the furano group. However, there has been little effort directed toward empirical correlations between given bands and specific furan hydrogens.

As a result of synthetic work directed toward furanocoumarins and other benzofuran derivatives, we have been able to gather and study the infrared spectra of a number of simple and complex substituted benzofurans. The findings of this study seem to indicate a relationship between the presence or absence of furan hydrogens and medium to strong bands in the 1180–1020-cm.$^{-1}$ region. It is not surprising that a relationship exists since Katritzky and Lagowski[9] have shown that in the six-membered ring heteroaromatic series, and presumably in the five-membered series as well, the number and relative orientations of the hydrogen atoms determine the positions of the in- and out-of-plane bending modes. The strong absorption of the out-of-plane bending modes of aromatic hydrogen have long been used to establish substitution patterns while the in-plane bending modes are not of much diagnostic use because they usually give only weak bands and there are other types of absorption in the same region.

(1) L. H. Briggs and L. D. Colebrook, J. Chem. Soc., 2458 (1960).
(2) A. R. Katritzky and J. M. Lagowski, ibid., 657 (1959).
(3) T. Kubota, Tetrahedron, 4, 68 (1958).
(4) A. H. J. Cross, S. G. E. Stevens, and T. H. E. Watts, J. Appl. Chem. (London), 7, 562 (1957).
(5) L. W. Daasch, Chem. Ind. (London), 1113 (1958).
(6) A. H. J. Gross and T. H. E. Watts, ibid., 1161 (1958).
(7) A. Quilico, F. Piozzi, and M. Pavan, Tetrahedron, 1, 177 (1957).
(8) R. Royer, E. Bisagui, C. Hudry, A. Cheutin, and M. L. Desvaye, Bull. soc. chim. France, 1003 (1963).
(9) A. R. Katritzky and J. M. Lagowski, J. Chem. Soc., 4155 (1958).

The C–H in-plane bending bands (1270–1015 cm.$^{-1}$) of furans are much stronger and more easily distinguished than those for the more normal aromatic compounds presumably due to the polar nature of the hetero atom.

The compounds studied were divided into two groups. One group (Table I) included only substances with two

TABLE I
BENZOFURAN DERIVATIVES WITH TWO FURAN HYDROGENS

	←————Compd.————→			←——Bands (cm.$^{-1}$)——→	
R_1	R_2	R_3	R_4	$H\alpha$	$H\beta$
H	H	H	H	1029 (s)	1125 (s)
OH	H	H	COCH$_3^a$	1047 (m)	1138 (m)
H	H	OCH$_3$	Et^a	1048 (ms)	1142 (s)
H	H	OH	COCH$_3^a$	1073 (m)	1160 (ms)
H	OCH$_3$	OCH$_3$	H^b	1045 (m)	1139 (s)
H	OH	COCH$_3$	H^c	1042 (m)	1139 (s)
H	OH	COOH	H^c	1041 (s)	1140 (s)
OH	OCH$_3$	OCH$_3$	H^d	1087 (m)	1134 (s)
OOCCH$_3$	OCH$_3$	OCH$_3$	H^d	1070 (m)	1136 (s)
OCH$_3$	OH	COCH$_3$	OCH$_3^{e,f}$	1064 (s)	1143 (ms)

^{a} P. K. Ramachandran, A. T. Tefteller, G. O. Paulson, T. Cheng, C. T. Lin, and W. J. Horton, J. Org. Chem., 28, 398 (1963). ^{b} Unpublished work by P. K. Ramachandran and W. J. Horton. ^{c} P. K. Ramachandran, T. Cheng, and W. J. Horton, J. Org. Chem., 28, 2744 (1963). ^{d} Unpublished work of C. T. Lin and W. J. Horton. ^{e} Unpublished work of E. Paul and W. J. Horton. ^{f} Spectrum run in carbon tetrachloride.

furan hydrogens. This group had two bands, one in the range 1160–1125 cm.$^{-1}$ and one in the 1087–1029-cm.$^{-1}$ region which we suggest are associated with the in-plane bending modes of the β- and α-hydrogens on the furan nucleus and tend to be characteristic of furans with adjacent α- and β-hydrogens. The second group (Table II) has compounds with only a single furan hydrogen and in the β-position. These compounds all showed a band in the range 1172–1121 cm.$^{-1}$ and no medium or strong, sharp bands in the 1087–1029-cm.$^{-1}$ region which we feel is characteristic of the β-hydrogen.

It is not known if this generalization can be applied to simple furan derivatives but Quilico, Piozzi, and Pavan[7] report that dendrolosin and tetrahydrodendrolosin, both monosubstituted furan derivatives, do have medium to strong bands at 1156 and 1075 cm.$^{-1}$.

Since the region of the spectrum under consideration is one where many types of absorptions occur, the generalization discussed above should be used cautiously and perhaps in a negative sense rather than a positive one, i.e., the absence of a 1160–1125- or 1087–1020-cm.$^{-1}$ band indicating the lack of an α- or β-H on a benzofuran nucleus, rather than the occurrence of the proper absorption indicating the definite presence of the α- or β-H.

Experimental

All the infrared spectra were taken on a Beckman IR 5 with sodium chloride optics. Chloroform was used as solvent unless