Anal. Calcd for $C_{12}H_9NS$: C, 72.32; H, 4.55; N, 7.03; S, 16.09. Found: C, 72.25; H, 4.53; N, 7.19; S, 16.03.

Ultraviolet-visible spectrum gave $\lambda_{max}^{95\%EtOH}$ 228 mμ (log ε 4.23), 275 (4.59), 300 (4.14), 359 (3.47) sh, 413 (3.48).

The nmr spectrum showed H-1 at δ 8.76 (doublet, J_{14} = 3.0 cps), H-4 at δ 8.27 (doublet, J_{34} = 9.5 cps), H-3, -7, -8, and -9 as a multiplet from δ 8.00 to 7.20, and the CH_3 at δ 2.82.

8-Nitrothiapyrano[4,3-*b*]indole (9h).—Dehydrogenation of 2.35 g of **8h** with 4.56 g of dicyanodichloroquinone in 200 ml of refluxing xylene for 3 hr similarly gave a dark, insoluble complex which was decomposed by stirring for 24 hr with 10% sodium hydroxide solution. The yellow-brown alkali-insoluble product (0.5 g) was sublimed at 220° (0.6 mm) to give 0.35 g (15%) of pure **9h** as yellow crystals, mp 272–273°.

Anal. Calcd for $C_{11}H_6N_2O_2S$: C, 57.38; H, 2.63; N, 12.17; S, 13.93. Found: C, 57.52; H, 2.74; N, 11.82; S, 13.72.

Ultraviolet-visible spectrum showed $\lambda_{max}^{95\%EtOH}$ 273 mμ (log ε 4.48), 320 (3.89), 398 (3.55).

Because of the low solubility of this compound its nmr spectrum could not be measured in $CDCl_3$ for direct comparison with the other members of the series.

Registry No.—**8a**, 7076-17-7; **8c**, 14120-24-2; **8d**, 14120-25-3; **8e**, 14120-26-4; **8f**, 14120-27-5; **8g**, 14120-28-6; **8h**, 14120-29-7; **9a**, 244-75-7; **9b**, 14120-30-0; **9c**, 14120-31-1; **9d**, 14120-32-2; **9e**, 14120-33-3; **9f**, 14120-34-4; **9g**, 14120-35-5; **9h**, 14120-36-6; **11** (X = Cl[11]), 14120-37-7.

Acknowledgments.—We are indebted to the Warner-Lambert Research Institute for generous financial support of this work, to Dr. V. B. Fish of Lehigh University for the microanalyses, and to the National Science Foundation for a grant to purchase the nmr spectrometer.

Structure and Stereochemistry of the Benzilic Acid Rearrangement Product of 3α,17β-Diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one[1]

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The formation of 3α,11α,17β-trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone from 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one in a benzilic acid rearrangement required that the latter be preceded by a retro-aldol condensation leading to epimerization at C_{13} of the starting diketone. The stereochemical formulation of the lactone was based on spectral, thermodynamic, and mechanistic considerations. The stepwise degradation of the lactone to 3α,17β-dihydroxy-13α-C-nor-5β-androstan-11-one furnished chemical proof for its structure.

As a part of a continuing effort[2] to study the structural alteration of natural steroids, this report deals with an attempt to alter ring C in the 5β-androstane series.

A mixture of the known 11α- and 11β-bromo-3α,17β-diacetoxy-5β-androstan-12-one (**2a** and **2b**), obtained from 3α,17β-diacetoxy-5β-androstan-12-one (**1**) by bromination,[3] was treated with sodium hydroxide in aqueous methanol to afford the new 3α,12β,17β-trihydroxy-5β-androstan-11-one (**3a**) as the main product of the reaction. Oxidation of this triolone with bismuth trioxide in acetic acid solution[4] yielded 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (**5a**). The new enolic diketone absorbed in the ultraviolet at 282 nm (ε 9600),[5] and in its nmr spectrum the expected C_{10} methyl proton absorption at 73 cps[6] was observed. Two by-products from this oxidation mixture were demonstrated to be the triacetate **3b**, identical with that obtained by acetylation of **3a**, and the diacetate **3c** which upon acetylation furnished **3b**. The nmr spectrum of the strongly hydrogen bonded 12-equatorial monohydroxy compound **3c** was of interest since the hydroxyl proton and the 12-axial proton formed an isolated AB system giving rise to an AB quartet with the OH doublet and the 12α-H doublet appearing at 212 and 238 cps, respectively (J_{AB} = 4.5 cps).[7] After the addition of deuterium oxide, the axial proton at C_{12} absorbed as a singlet at 239 cps. This observation confirmed the 12-hydroxy-11-oxo structure; the C_{11} proton of an 11-hydroxy-12-oxo compound would be coupled with the proton at C_9 and a more complex nmr pattern could be expected.

Since the triolone **3a** was obtained by alkali treatment of a mixture of the 11α- and 11β-bromo 12-ketones **2a** and **2b**, the possibility of epimerization at C_{13} by a retro-aldol condensation, similar to that postulated below, had to be considered. For that reason it was necessary to investigate the stereochemistry of this intermediate. Its triacetate **3b** was reduced with calcium in liquid ammonia[8] and the resulting product was acetylated to yield the known[9] 3α,17β-diacetoxy-5β-androstan-11-one (**4**). This finding allows the assignment of the stereochemistry of the natural steroids at C_{13} to the triacetate **3b**, the diacetate **3c**, the triolone **3a**, the oxidation product **5a**, and its derived acetate **5b**.

The attempted reduction of the 12-acetoxy group of **3b** with zinc dust in acetic acid[10] was shown to lead to the almost quantitative recovery of the starting material. This finding supported the assignment of the

(1) A preliminary report of this work has appeared: P. Kurath, *Experientia*, **22**, 657 (1966).

(2) P. Kurath, W. Cole, J. Tadanier, M. Freifelder, G. R. Stone, and E. V. Schuber, *J. Org. Chem.*, **28**, 2189 (1963).

(3) P. L. Julian and A. Magnani, U. S. Patent 2,940,991 (1960).

(4) C. Djerassi, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5533 (1954); E. J. Becker and A. Cohen, U. S. Patent 3,185,713 (1965).

(5) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1949, p 195.

(6) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(7) (a) E. J. Becker, R. M. Palmere, A. I. Cohen, and P. A. Diassi, *J. Org. Chem.*, **30**, 2169 (1965); (b) A. I. Cohen, B. T. Keeler, E. J. Becker, and P. A. Diassi, *ibid.*, **30**, 2175 (1965); *cf.* A. Lablache-Combier, B. Lacoume, and J. Levisalles, *Bull. Soc. Chim. France*, 897 (1966).

(8) J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(9) L. H. Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).

(10) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **73**, 2403 (1951); **74**, 4223 (1952).

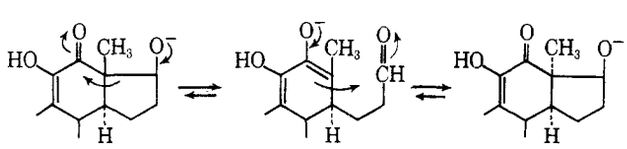
12β-equatorial configuration to the acetoxy group next to the keto group in **3b**, since the axial 12α-acetoxy 11-ketone would be expected to be reduced by this method. It was observed earlier that zinc deacetylation of the axial 12α-acetoxy group in methyl 3α,12α-diacetoxy-11-ketocholanate proceeded much more readily than with the equatorial 12β-acetoxy derivative.[11] The observation that the most abundant ketol formed in the alkali equilibration had the 12β-hydroxy-11-oxo structure was expected in view of earlier reports in the literature.[12]

When the solution of 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (**5a**) in aqueous propanol containing potassium hydroxide was warmed to a gentle reflux, conditions which in the case of a steroidal 2,3-diketone gave rise to a benzilic acid rearrangement,[13] a new compound was isolated after a work-up which included acidification of the alkaline reaction mixture. The new substance, obtained in 76% yield, was found to analyze for $C_{19}H_{28}O_4$ (**6a**), it showed only end absorption in the ultraviolet, and its infrared spectrum revealed bands for hydroxyl (3600 cm^{-1}) and carbonyl (1755 cm^{-1}). Acetylation of **6a** led to the formation of a diacetate, $C_{23}H_{32}O_6$ (**6b**), which no longer showed a hydroxyl absorption in the infrared while the oxidation with Jones reagent[14] yielded a monoketone, $C_{19}H_{26}O_4$ (**7a**). The infrared spectrum of the oxidation product revealed bands for hydroxyl (3578 cm^{-1}), the original carbonyl (1755 cm^{-1}), and the newly introduced keto group (1700 cm^{-1}). The above ketone **7a** furnished a monoacetate, $C_{21}H_{28}O_5$ (**7b**). The fact that only one of the two hydroxyl groups of **6a** could be oxidized suggested that the second hydroxyl group was tertiary, a conclusion which was further supported by the observation that **6a** formed only a mono-*p*-bromobenzoate **6c**.

Evidence for the proximity of the nonoxidizable hydroxyl group to the carbonyl function absorbing at 1755 cm^{-1} was obtained when the infrared spectra of the dihydroxy compound **6a** and the hydroxy ketone **7a** were recorded in 0.00125 *M* carbon tetrachloride solutions. The spectrum of the diol **6a** revealed absorptions for both the free and the intramolecularly bonded hydroxyl ($\tilde{\nu}_{max}$ 3620, 3575 cm^{-1}) while the spectrum of the ketone **7a** showed only the intramolecularly bonded hydroxyl ($\tilde{\nu}_{max}$ 3573 cm^{-1}).[15] It was expected that the absorption of the carbonyl group functioning as the proton acceptor would be shifted as a consequence of intramolecular hydrogen bonding.[16] The elimination of the intramolecular hydrogen bonding by acetylation of the hydroxy carbonyl compounds **6a** and **7a** was accompanied by a shift in the infrared spectrum of the intramolecularly hydrogen-bonded carbonyl absorption at 1755–1770 cm^{-1} in the case of the acetates **6b** and **7b** where intramolecular hydrogen bonding was no longer possible. The hypsochromic shift of 15 cm^{-1} indicated that the hydroxyl group responsible for the intramolecular hydrogen bonding was attached to either the α- or the β-carbon relative to the carbonyl group.[16]

The above observations allowed the conclusion that the reaction product $C_{19}H_{28}O_4$ which was isolated after the alkali treatment of **5a** and subsequent acidification of the reaction mixture during work-up had a secondary hydroxyl group, a tertiary hydroxyl group α or β to a carbonyl function and an oxygen function that was inert toward both acetylation and oxidation. The molecular formula $C_{19}H_{28}O_4$, together with the evidence of the presence of a carbonyl group, allowed the conclusion that the sum of the remaining rings and double bonds was five.[17] The finding that, aside from the above-mentioned carbonyl function, no evidence of unsaturation could be discovered led to the conclusion that the new compound had a pentacyclic structure and that the "inert oxygen" was part of a ring. The nature of the oxygen functions and the observation that the compound $C_{19}H_{28}O_4$ was alkali soluble and ether extractable after acidification of the solution suggested the possibility that the compound was a lactone. The ease of formation of **6a**, together with the infrared absorption of the carbonyl group, indicated that the lactone in question was probably a γ-lactone which was part of an unstrained system. The presence of a tertiary hydroxyl group α to the carbonyl function would suggest that a benzilic acid rearrangement of **5a** had indeed occurred and that the newly formed carboxyl group became part of a lactone.

This working hypothesis led to the examination of the possibility of γ-lactone formation of a benzilic acid rearrangement product of **5a**. For stereochemical reasons it was found to be impossible for a benzilic acid rearrangement product of **5a** with the *trans*-fused C–D rings to form an 11a,17-lactone; the distance between either an 11α- or an 11β-carboxyl group and the 17β-hydroxyl group was found to be too large for the formation of a lactone bridge. Facile lactone formation in a strain-free all-*cis*-fused system containing three five-membered rings[18] would be feasible if the C–D rings were *cis*-fused and the carboxyl group at C_{11} and the hydroxyl group at C_{17} were oriented *trans* to the angular methyl group at C_{13}. For this reason an additional retro-aldol equilibrium of the potential β-hydroxy ketone **5a** was postulated to lead to epimerization at C_{13} as formulated below. The formation of the *cis*-fused C–D ring system would precede the



benzilic acid rearrangement of the α-diketone. The ginkgolides, a group of natural products, were recently shown to contain as part of their structure three five-membered rings, one of which is a lactone,

(11) R. S. Rosenfeld and T. F. Gallagher, *J. Am. Chem. Soc.*, **77**, 4367 (1955); *cf.* F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *ibid.*, **75**, 4712 (1953).

(12) L. F. Fieser, *Experientia*, **6**, 312 (1950); ref 7a and footnotes 4c and 7 therein.

(13) H. R. Nace and D. H. Nelander, *J. Org. Chem.*, **29**, 1677 (1964).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

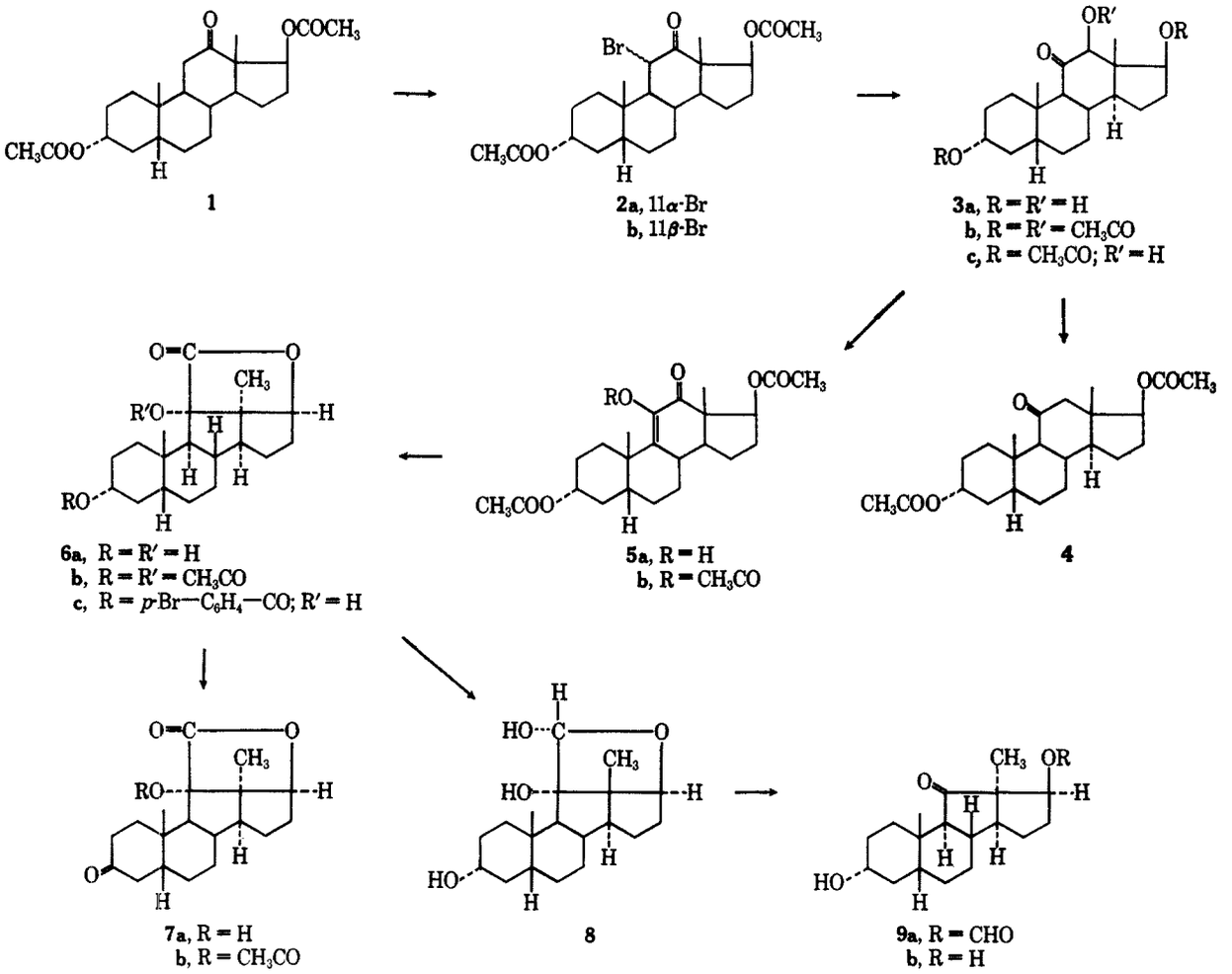
(15) M. Tichy in "Advances in Organic Chemistry: Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, pp 119, 162, and 210.

(16) G. Eglinton in "Physical Methods in Organic Chemistry," J. C. P. Schwarz, Ed., Holden-Day, Inc., San Francisco, Calif., 1964, pp 66–68, 74; ref 15, p 119.

(17) *Cf.* L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corporation, New York, N. Y., 1961, p 178.

(18) R. Adams and N. J. Leonard, *J. Am. Chem. Soc.*, **66**, 257 (1944), reported the all *cis*-fused anhydroplatynecine.

SCHEME I



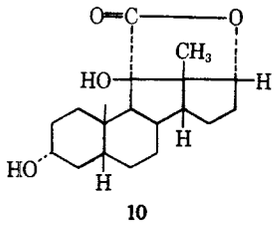
joined together in an all-*cis*-fused system[19] analogous to the one proposed above.

The above considerations led to the formulation of the reaction product resulting from the alkali and subsequent acid treatment of **5a** as 3α,11α,17β-trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone (**6a**) (Scheme I). The acetylation product of **6a** was then assigned the diacetate structure **6b**.[20] It was reasonable to assume that mono-*p*-bromobenzoylation would lead to esterification of the secondary rather than the teritary hydroxyl group to furnish **6c**. Oxidation of **6a** led to 11α,17β-dihydroxy-3-oxo-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone (**7a**) which upon acetylation yielded the 11α-acetate **7b**. The above formulations explained all the observed physical and chemical properties of the compounds discussed. The nmr and mass spectra of these compounds, to be presented below, likewise fully supported these structural assignments.

Thus far the stereochemical assignments at C_{11}, C_{13}, C_{14}, and C_{17} of the lactone **6a** and its derivatives have been discussed. Since, during the rearrangement in the C–D ring region of **5a**, intermediates were involved which could affect the stereochemistry at the B–C ring junction, it was necessary to consider this structural aspect. The study of Dreiding molecular models led to the conclusion that the most desirable stereochemistry at C_8 and C_9 of the rearrangement product was that found in the natural steroids and consequently the hydrogen atoms at the B–C ring junction of **6a** were postulated to have the 8β,9α configuration. A somewhat less satisfactory spatial arrangement and therefore a less probable structure of the rearranged molecule resulted when the 8α,9β configuration was assigned to the hydrogen atoms at the B–C ring junction of the rearranged substance. In the two possible cases of *cis* fusion between rings B and C (8α,9α and 8β,9β) severe steric interactions led to untenable arrangements.

(19) M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, Y. Takagi, and K. Nakanishi, *Tetrahedron Letters*, 315 (1967), and accompanying papers; N. Sakabe, S. Takada, and K. Okabe, *Chem. Commun.*, 259 (1967).

(20) The asymmetric center at C_{14}, situated in the allylic position of the α,β-unsaturated keto system of the 13,17-seco aldehyde (retro-aldol equilibrium above), could be epimerized and an aldol condensation followed by a benzilic acid rearrangement could give rise to a second possible structure, **10**, which would satisfy the stereochemical requirements for γ-lactone formation. Examination of Dreiding molecular models indicated severe steric inhibition to acetylation of the 11β-hydroxyl of **10** while the sterically less hindered 11α-hydroxy compound **6a** could be visualized to form the diacetate **6b**.



10

The isolation of lactone **6a** in 76% yield upon acidification of the reaction mixture resulting from the potassium hydroxide treatment of **5a** allowed the conclusion that the retro-aldol equilibrium formulated above was shifted toward the thermodynamically more stable C–D ring *cis*-fused intermediate derived from **5a**. The ring strain imposed on the hydrindane part of the molecule by the presence of the enolized α-diketone system in **5a** was apparently smaller in the C–D ring *cis*-fused structure than in the parent compound **5a** where the C–D rings were *trans* fused. Examples reported in the literature clearly indicate that the relative stabilities of C–D *cis*- and *trans*-fused steroidal compounds are dependent on their substituents.[21] A recent publication furnished an account of a retro-aldol equilibrium of a bicyclic β-hydroxy ketone which led to a mixture containing a preponderance of the thermodynamically more stable equatorial epimer of the alcohol.[22]

Chemical proof of the structure **6a** resulted from the stepwise degradation of the lactone **6a** to 3α,17β-dihydroxy-13α-C-nor-5β-androstan-11-one (**9b**). Lithium aluminum hydride reduction of **6a** led to the isolation of a single reduction product which was formulated as the hemiacetal **8** when it was discovered that lead tetraacetate oxidation of the latter yielded the formate **9a**. The infrared spectrum of **8**, when determined in dilute carbon tetrachloride solutions, revealed strong intramolecular hydrogen bonding which was attributed to the *cis*-oriented 11α- and 11aα-dihydroxy system in the five-membered ring. It was reported that *cis*-1,2-diols in five-membered rings showed intramolecular hydrogen bonding while the corresponding *trans*-1,2-diols revealed only the absorption of the nonbonded hydroxyl group.[23] The formate **9a**, which was recognized by its characteristic spectral properties, upon mild hydrolysis gave rise to the C-nor-diolone **9b**. Only one of the two possible C_9-epimeric C-nor ketones was obtained (60% yield) from the lactone **6a**.

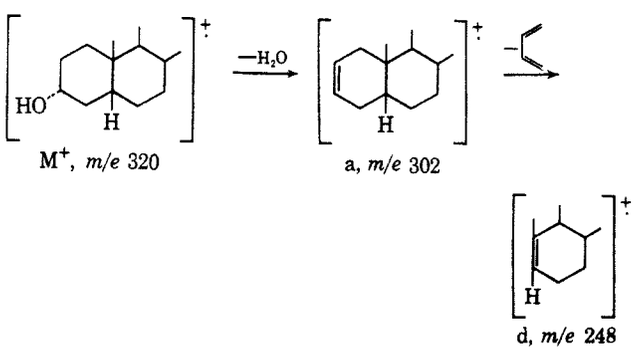
The presence of the 11-keto group in the degradation product **9b** necessitates consideration of the possibility of epimerization at C_9. Some related C–D *trans*-fused C-nor-11-ketones in both the 5α and the 5β series have been described.[24] The criteria presented in the discussion of the 5β series by the French workers appeared to be applicable to the situation where the C–D rings are *cis* fused. Both the 9α and the 9β epimer may have chair form A and B rings. Because of the rigidity and deformation of the molecule in the 9β-epimer, C_{10} with its three substituents (C_1, C_5, and C_{19}) is forced into an axial orientation with respect to the C ring. In addition, C_1 and C_{14} are axial relative to the B ring, and the angular methyl group at C_{13} is forced into close proximity with the C_1-methylene group. These unfavorable steric interactions are not present in case of the 9α-epimer and thus the B–C ring junction of **9b** is formulated as 8β,9α.

The study of the mass spectra of the lactones **6a**, **6b**, **7a**, and **7b** established the structural identity of the A–B ring system of the benzilic acid rearrangement product **6a** and its derivatives and gave evidence for the lactone structure in the above compounds.

The mass spectrum of **6a** (Figure 1) revealed the molecular ion peak at *m/e* 320, and two prominent peaks at *m/e* 302 (a) and *m/e* 284 (b) were due to the sequential loss of two molecules of water from the molecular ion of **6a**. This was confirmed by the occurrence of two metastable peaks at *m/e* 285.0 ($302^2/320 = 285.0$) and *m/e* 267.0 ($284^2/302 = 267.1$). A peak at *m/e* 273 (c) was shown to correspond to an ion derived from a by the loss of 29 mass units by the observation of a metastable peak at *m/e* 247.0 ($273^2/302 = 246.8$). This fragmentation may be due to the expulsion of the elements of HCO from the lactone moiety of the ion a.[25] The ionized olefin a decomposed through a retro-Diels–Alder reaction[26,27] to afford d (*m/e* 248) which formed e (*m/e* 230) by elimination of water and finally f (*m/e* 215) by loss of a methyl radical from e.

The mass spectral cleavage pattern of the diacetate **6b** was found to be similar to that of the diol **6a**. The loss of two molecules of acetic acid from the molecular ion of **6b** (*m/e* 404, 7.8%) led to abundant ions of *m/e* 344 (a',[28] 100%) and *m/e* 284 (b, 91%). This fragmentation caused the appearance of two metastable peaks at *m/e* 293.0 ($344^2/404 = 292.9$) and 234.5 ($284^2/344 = 234.5$). Only a minor peak appeared at *m/e* 290 (d', 3.2%) where the ion resulting from the retro-Diels–Alder reaction[26] of a' would be expected to be detected. However, a more intense peak at *m/e* 230 (e, 19%) resulted from the retro-Diels–Alder reaction[26] of b. A peak of low intensity at *m/e* 215 (f, 5.5%) corresponded to the expulsion of a methyl radical from e. A minor peak at *m/e* 386 (4.8%) was due to the elimination of water from the lactone moiety of the molecular ion of **6b** in a complex process.[25] Two larger peaks at *m/e* 302 (43%) and 258 (46%) appear to be characteristic of **6b**.

In the mass spectrum of the keto lactone **7a** (Figure 2) the molecular ion at *m/e* 318 was found to eliminate



M^+, *m/e* 320 a, *m/e* 302 d, *m/e* 248

(21) A. R. Van Horn and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 651 (1967), and ref 4–7 given therein.

(22) J. Martin, W. Parker, B. Shroot, and T. Stewart, *J. Chem. Soc., C*, 101 (1967).

(23) Reference 15, pp 173, 174.

(24) J. Winter, M. Rajić, and G. Ourisson, *Bull. Soc. Chim. France*, 1363 (1964).

(25) E. Honkanen, T. Moisio, and P. Karvonen, *Acta Chem. Scand.*, **19**, 370 (1965).

(26) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, Inc., San Francisco, Calif., 1964, p 103. (b) One of the referees pointed out that the formulation of the mass spectral cleavage of water from the molecular ion of **6a** (M^+) to the Δ^2-olefin a and the subsequent formulation of the retro-Diels–Alder cleavage product d from a "is not too certain in view of the fact that 3α- and 3β-hydroxy steroids in the 5α-series do not lose water to give Δ^2-olefins unless it is a thermal process."[27] This observation is applicable to all such formulations within this paper. However, the formal loss of the elements of water followed by the elimination of the elements of butadiene from 3α-hydroxy 5β-steroids appears to be characteristic of this group of compounds.

(27) J. Karliner, H. Budzikiewicz, and C. Djerassi, *J. Org. Chem.*, **31**, 710 (1966).

(28) The ion a' from **6b** corresponds to the related ion a formed from **6a**.

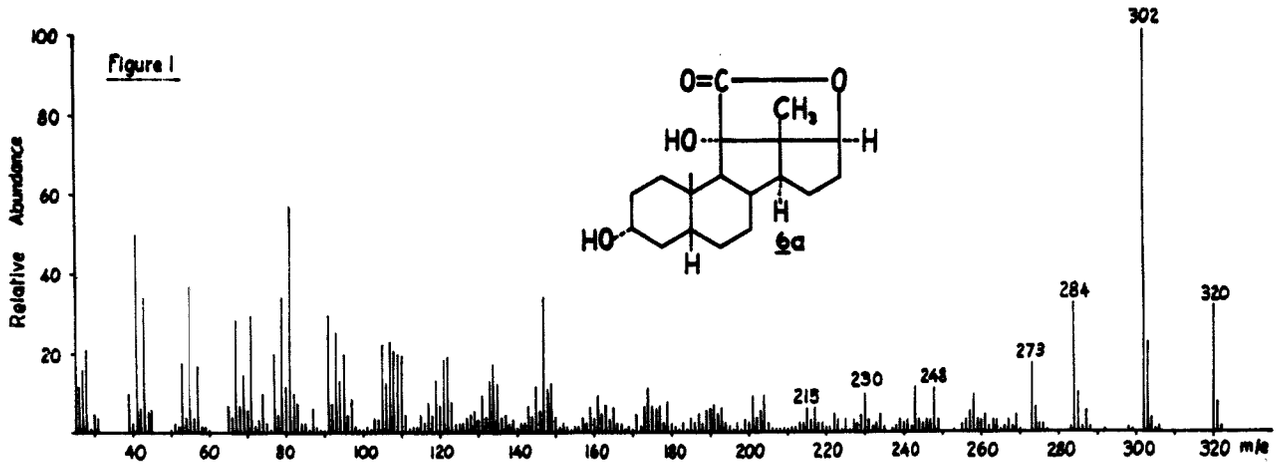


Figure 1.—Mass spectrum of 3α,11α,17β-trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone (6a).

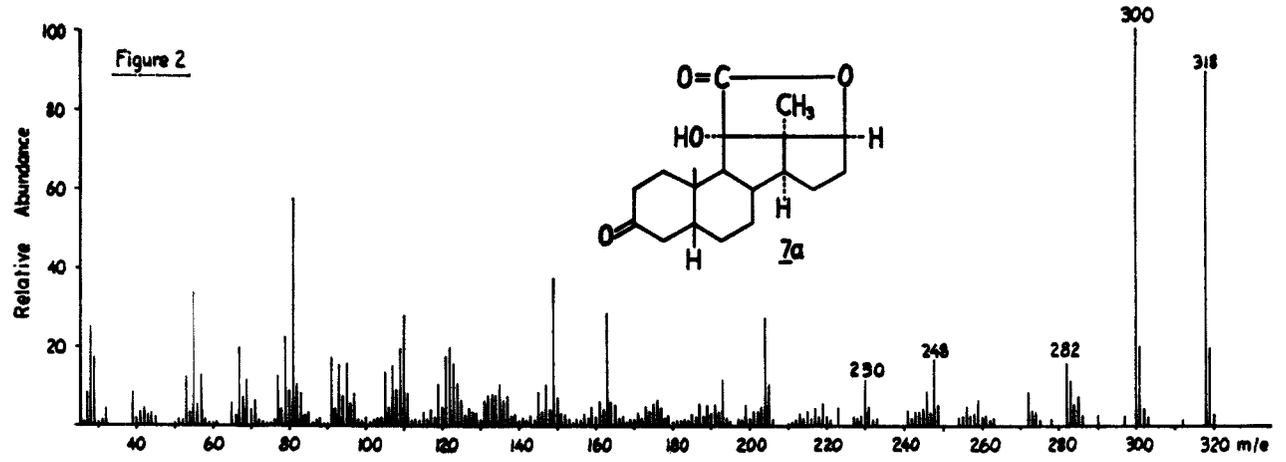
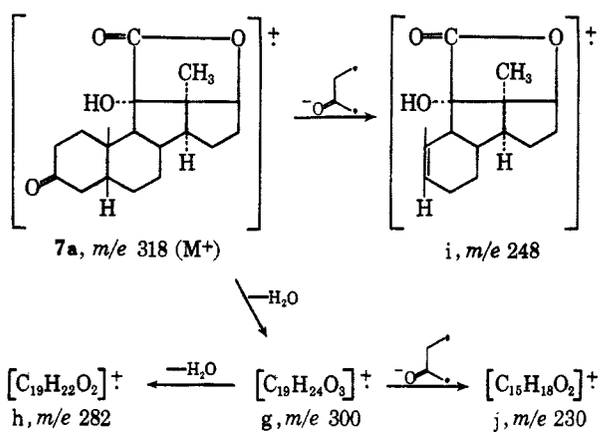


Figure 2.—Mass spectrum of 11α,17β-dihydroxy-3-oxo-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone (7a).

water, giving rise to an ion at 300 (g) and a corresponding metastable peak at 283.0 ($300^2/318 = 283.0$). A less abundant ion at *m/e* 282 (h) resulted from the loss of a molecule of water from g. A metastable peak at *m/e* 265.0 ($282^2/300 = 265.1$) further supported this fragmentation. The loss of the elements of water from ketones has been frequently reported[29] and the ion h is probably derived from the ketone portion of g. Two peaks at *m/e* 248 (i) and 230 (j) represented the loss of 70 mass units from the molecular ion (*m/e* 318) and the ion g (*m/e* 300), respectively. This type of fragmentation was found to be characteristic of the loss of the first four carbon atoms (C_1 through C_4) in a 3-keto-5β-H steroid under electron impact[30] (Scheme II).

The mass spectrum of the keto acetate **7b** was found to be similar to that of the corresponding keto alcohol **7a**. The molecular ion of the acetate **7b** at *m/e* 360 (51%) gave rise to an ion at *m/e* 342 (k, 3%) due to the loss of the elements of water from the ketonic portion[29] and to some extent to the loss of water from the lactone part[25] of **7b**. A second peak at *m/e* 318 (11%) was found to be 42 mass units lower than the molecular peak. The ion corresponding to the base peak at *m/e*

SCHEME II



300 (g) resulted from the elimination of acetic acid from the molecular ion of **7b**. In connection with this fragmentation, a metastable ion at *m/e* 250.0 ($300^2/360 = 250.0$) was observed. The less abundant ion at *m/e* 282 (h, 11%) resulted from the loss of water from the ketone portion[29] of g. The formation of h from g gave rise to a metastable ion at *m/e* 265.0 ($282^2/300 = 265.1$). Finally the ion j (*m/e* 230, 13%) arose from the ion g (*m/e* 300) by the loss of the first four carbon atoms of the 3-keto-5β-H structure[30] of g.

The interpretations of the mass spectral fragmentations of the above lactones (**6a**, **6b**, **7a**, **7b**) was com-

(29) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 1; (b) *cf.* E. Lund, H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 941 (1963); C. Djerassi and L. Tökés, *ibid.*, **88**, 536 (1966).

(30) H. Budzikiewicz and C. Djerassi, *ibid.*, **84**, 1430 (1962).

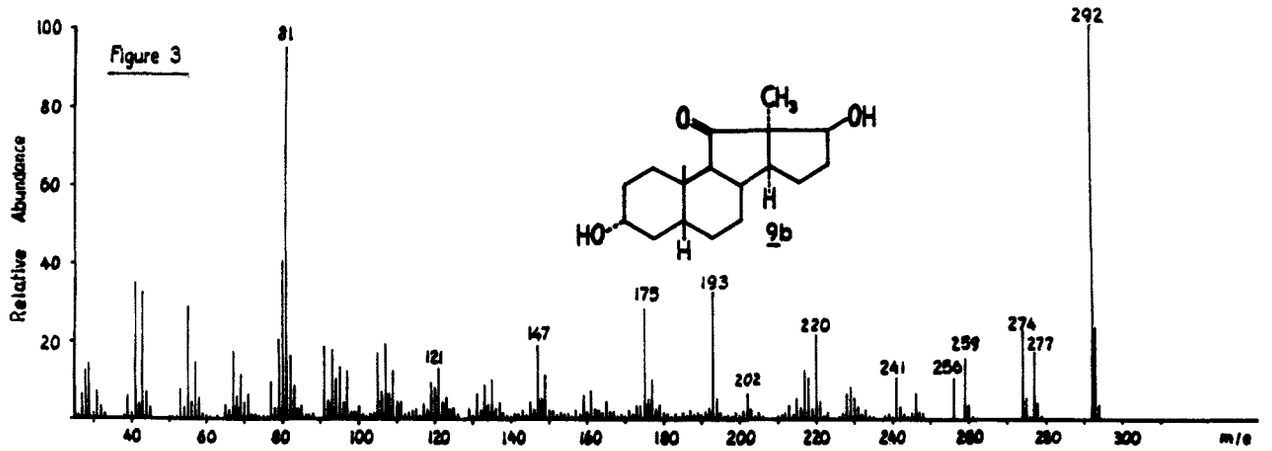


Figure 3.—Mass spectrum of 3α,17β-dihydroxy-13α-C-nor-5β-androstan-11-one (9b).

plicated by the fact that these compounds contained the three fused five-membered rings in the C–D ring region. However, the spectra clearly established that the 3α-OH group and the A–B ring system were not involved in the rearrangement that led to the disappearance of the ring C chromophore during the alkali treatment of **5a**.

The mass spectrum of the degradation product **9b** (Figure 3) could readily be explained in terms of the structural features of the diolone. The base peak in the mass spectrum of the C-nor ketone **9b** at *m/e* 292 is that expected from the molecular ion. The ions at *m/e* 277 (l, M − 15), 274 (m, M − 18), 259 (n, M − 18 − 15), 256 (o, M − 36), and 241 (p, M − 36 − 15) arose from the possible combinations of the loss of one angular methyl group and/or one or both hydroxyls in the form of water. The formation of the above ions gave rise to metastable ions at *m/e* 263.0 ($277^2/292$ = 262.8), 257.0 ($274^2/292$ = 257.1), 242.0 ($259^2/277$ = 242.2), 239.1 ($256^2/274$ = 239.2), and 224.5 ($241^2/259$ = 224.3).

A first group of cleavage products resulted from the electron impact fragmentation in the A-ring region (Scheme III). The peak at *m/e* 220 was due to the ion q which arose by the formal loss of butadiene in a retro-Diels–Alder reaction[26] from m. This cleavage led to the observation of a metastable peak at *m/e* 176.4 ($220^2/274$ = 176.6). The elimination of the elements of water from q gave rise to the ion r as shown by the peak at *m/e* 202; a metastable ion at *m/e* 185.5 ($202^2/220$ = 185.5) was associated with this reaction.

A second group of fragment ions resulted from the initial α cleavage of the C_{11}–C_{13} bond in the ketone **9b** to afford s (*m/e* 292) in which the hydrogen on C_9 was shifted to the radical site at C_{13} followed by homolytic cleavage of the C_8–C_{14} bond[31] to furnish the ion t. The latter gave rise to a peak at *m/e* 193 and to a metastable ion at *m/e* 127.5 ($193^2/292$ = 127.6) which further supported the proposed fragmentation. The elimination of water from t led to u (*m/e* 175) and a metastable ion with *m/e* 158.5 ($175^2/193$ = 158.7). The loss of carbon monoxide from u and migration of the angular methyl group to C_9[32] gave v (*m/e* 147), while the retro-Diels–Alder reaction[26] of u afforded w (*m/e* 121). Elimination of the 17-OH group in s led to the even electron fragment x (*m/e* 275) in which the C_8–C_{14} bond was cleaved heterolytically to yield the hydrocarbon ion y (*m/e* 81) derived from the D ring. The appearance of a metastable peak at *m/e* 24.0 ($81^2/275$ = 23.9) lent support to this simple explanation of the formation of the resonance-stabilized allylic ion y which may account for its high abundance.

Relatively intense peaks at *m/e* 81 which were also observed in the mass spectra of the above lactones may have resulted from a similar cation.

Additional support for the structure of the rearrangement product **6a** and its derivatives **6b**, **7a**, and **7b**, as well as the degradation products **8**, **9a**, and **9b**, was obtained by examination of their nmr spectra. The relevant data are recorded in Table I.

TABLE I
PROTON MAGNETIC RESONANCE SPECTRA[a]

Compound	17α-H[b]	17α-H, half-width[c]	3β-H[b]	3β-H, half-width[c]	Angular methyl	Acetate methyl
6a	258	13	218	18	60, 67	...
6b	275	14	285[d]	18[d]	64, 64	123, 126
7a	259	12	...	...	64, 68	...
7b	275	11	...	...	65, 69	127
8	252	8	214	20	62, 65	...
9a	306	7	215	20	60, 70	...
9b	238	9	215	18	59, 67	...

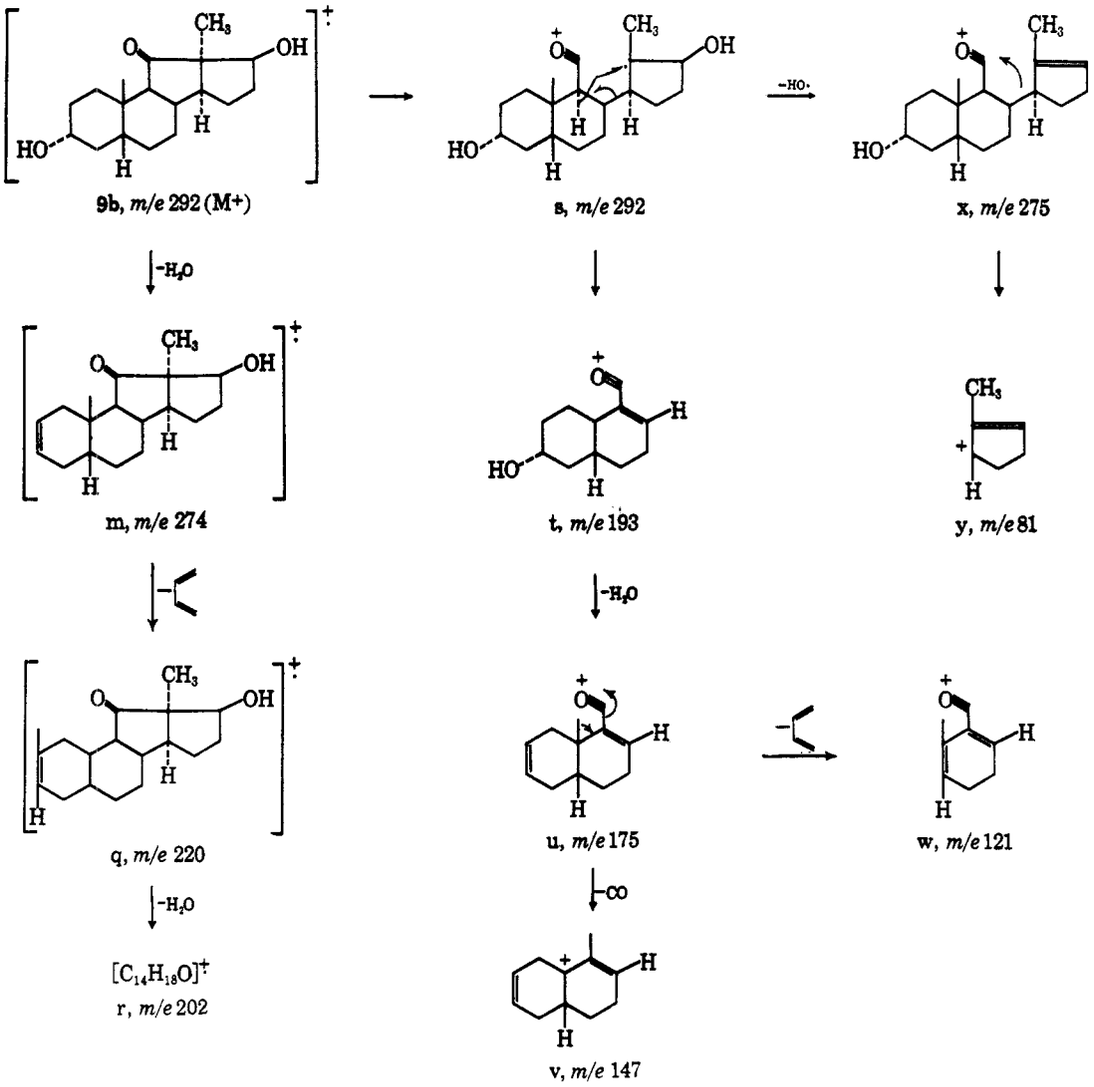
[a] The spectra were recorded with a Varian A-60 nmr spectrometer at 60 Mc; 5–10% solutions in deuteriochloroform were employed using tetramethylsilane as an internal reference. Chemical shifts are reported in cps from tetramethylsilane (0 cps) in the direction of decreasing field. [b] Multiplet. [c] Half-width indicates the width (in cps) of the band at half its height. [d] Estimated.

The nmr spectra of the hydroxy lactone **6a** and its oxidation product **7a** demonstrated that no change had taken place at C_{17} during the oxidation of **6a**. The 17α-proton absorptions of **6a** and **7a** appeared at 258 and 259 cps as complex multiplets with half-widths of 13 and 12 cps, respectively. In the region between 180 and 320 cps the spectrum of the keto lactone **7a** showed only the absorption envelope of the 17α-proton while the spectrum of **6a** revealed in addition the broad unresolved 3β-axial proton absorption which was centered at about 218 cps. This chemical shift was close to that reported for the 3β-axial proton of 3α-hydroxy-

(31) *Cf.* F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, p 137.

(32) L. Tökés and C. Djerassi, *Steroids*, **6**, 493 (1965). The author wishes to express his appreciation to referee I for calling his attention to the analogy of the cleavage u → v to that reported by Tökés and Djerassi.

SCHEME III



5β-androstan-11-one (214 cps).[33] The width at half-height of the absorption of the 3β-proton of **6a** (18 cps) was characteristic of axial protons.[34]

The signals of the 17α-protons of the acetates **6b** and **7b** were found to be complex multiplets appearing at 275 cps with half-widths of 14 and 11 cps, respectively. The downfield shifts of the 17α-proton absorptions in the spectra of the acetates **6b** and **7b** as compared to those of **6a** and **7a** are a consequence of the *cis* relationship of the deshielding 11α-acetoxy group and the 17α-proton. This finding is contrary to the observation that acetylation of certain hydroxyl groups was accompanied by a diamagnetic shift of the neighboring methyl proton absorptions of some steroids.[35] The difference in these findings must reflect the fact that the shielding or deshielding properties of the acetate carbonyl are dependent on the stereochemical arrangement. The observation that acetylation of a 6β-hydroxy-5β,19-cyclo steroid had little effect on the signals of the C_{19}-methylene protons[36] may be similarly explained. In the spectrum of the diacetate **6b**, the 17α-proton absorption partially overlapped the broad, unresolved 3β-axial proton absorption which was centered at about 285 cps. This chemical shift was in good agreement with the values reported for the 3β-axial protons of two 3α-acetoxy-5β-H steroids (283.8 and 282 cps).[37] The tertiary nature of the hydroxy and acetoxy groups at C_{11} of the lactones **6a**, **6b**, **7a**, and **7b** was confirmed by the absence of other absorptions in the region characteristic of protons attached to carbon atoms bearing hydroxy or acetoxy groups (180–320 cps).

The nmr spectrum of the reduction product derived from **6a**, the hemiacetal **8**, revealed a singlet at 338 cps which was due to the newly introduced 11aβ-proton. The 17α-proton signal was seen as a complex narrow multiplet centered at 252 cps, while the 3β-proton absorption was observed as a broad multiplet centered at 214 cps. The lead tetraacetate oxidation product of **8** was recognized as the formate **9a** by the signal at 474 cps which was due to the proton of the formyl group. The formyl-proton absorptions of methyl formate[38] and isopropyl formate[39] were reported to be at 484.8 and 481.2 cps, respectively. The signal of the

(33) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).
(34) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 109, 111.
(35) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).
(36) J. Tadanier, *J. Org. Chem.*, **31**, 2124 (1966).
(37) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectra No. 361 and 362
(38) Reference 37, Spectrum No. 9.
(39) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 415.

3β-axial proton remained practically unchanged as a broad absorption centered at 215 cps, while the 17α-proton absorption was found at 306 cps as a narrow (half-width 7 cps) complex multiplet which was shifted downfield relative to that observed for **8**. In the spectrum of the hydrolysis product **9b** the complex multiplet signal for the 17α-proton was centered at 238 cps (half-width 9 cps) while the broad absorption for the 3β-axial proton remained unchanged as compared to the corresponding signal of the ester **9a**.

A single-crystal X-ray analysis[40] on the 3-*p*-bromobenzoate of the rearrangement product (**6c**) determined the stereochemistry at the B–C ring junction, which was previously postulated to be that of the naturally occurring androstanes.[1] The X-ray study confirmed the unusual structure containing three five-membered rings in an all-*cis*-fused system.[1]

Experimental Section[41]

11α-Bromo- and 11β-Bromo-3α,17β-diacetoxy-5β-androstan-12-one (2a and 2b).—The known[3] 3α,17β-diacetoxy-5β-androstan-12-one (**1**) (6.070 g), mp 193–194°, $[\alpha]^{28}D$ +139° (*c* 1.048), was brominated according to the procedure of Julian and Magnani[3] to yield, after one recrystallization of the crude reaction product from ether–heptane, a mixture of 7.020 g of the 11α- and 11β-bromo ketones **2a** and **2b**,[3] mp 143–158°. Several recrystallizations of this mixture from ether–heptane and then from methanol yielded 1.315 g of 11α-bromo-3α,17β-diacetoxy-5β-androstan-12-one **2a**, mp 165–166°. An analytical sample had the following physical constants: mp 166–167°; $[\alpha]^{24}D$ +64° (*c* 1.153); $\bar{\nu}_{max}$ 1724 cm^{-1}; the nmr spectrum showed peaks at 289 cps (d, J = 10 cps) 11β-H.

Anal. Calcd for $C_{23}H_{33}BrO_5$: C, 58.85; H, 7.09. Found: C, 58.60; H, 6.96.

The early mother liquors of the above recrystallizations were concentrated and the resulting mixture was recrystallized several times from methanol to afford 0.435 g of analytically pure 11β-bromo-3α,17β-diacetoxy-5β-androstan-12-one (**2b**), mp 186–188°, $[\alpha]^{24}D$ +37° (*c* 1.065), $\bar{\nu}_{max}$ 1725 cm^{-1}; the nmr spectrum showed peaks at 260 cps (d, J = 4 cps) 11α-H.

Anal. Calcd for $C_{23}H_{33}BrO_5$: C, 58.85; H, 7.09. Found: C, 59.04; H, 7.12.

From the combined concentrated mother liquors of the 11α- and 11β-bromo 12-ketones 3.39 g of a mixture of **2a** and **2b**, mp 144–152°, was isolated. It was found that separation of **2a** and **2b** was not necessary for the preparation of **3a**.

3α,12β,17β-Trihydroxy-5β-androstan-11-one (3a).—A mixture of the bromo ketones **2a** and **2b**, 8.485 g, mp 140–145°, obtained from 8.100 g of **1** as described above, together with 9.80 g of sodium hydroxide pellets was dissolved in 230 ml of methanol and 28 ml of water. The resulting solution was stirred and warmed to a gentle reflux for 1 hr, and agitation was continued for 2 hr at room temperature.[42] The methanol was gradually evaporated under reduced pressure on the steam bath, and a total of 710 ml of water was added in portions. The resulting slurry was allowed to cool, and the precipitate was collected on a filter, washed with several small amounts of water, and dried overnight at 70° under reduced pressure. The dry residue, 4.883 g, was purified by chromatography on 500 g of silica gel. From the ethyl acetate–methanol (9:1) eluates[43] a residue amounting to 3.570 g of crude 3α,12β,17β-trihydroxy-5β-androstan-11-one (**3a**) was obtained. Recrystallization of this material from acetone gave 3.025 g (45% yield based on **1**) of the desired compound **3a**, mp 234–235°. Concentration of the mother liquors gave a second crop of 0.292 g, mp 228–232°.

A sample of the above first crop was recrystallized for analysis: mp 235–236°; $[\alpha]^{27}D$ +52° (*c* 0.546); $\bar{\nu}_{max}^{Nujol}$ 3410, 1690 cm^{-1}.

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.78; H, 9.38. Found: C, 70.51; H, 9.40.

3α,17β-Diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (5a).—The mixture of 4.490 g of 3α,12β,17β-trihydroxy-5β-androstan-11-one (**3a**), 8.85 g of bismuth trioxide, and 155 ml of glacial acetic acid was stirred and warmed to a gentle reflux for 22 hr.[4] The reaction mixture was cooled and the precipitate was collected on a filter. The contents of the filter were washed with 1200 ml of chloroform which was added to the above filtrate. The clear solution was washed with 500 ml of water, the layers were separated, and the aqueous phase was extracted with two 1200-ml portions of chloroform. The chloroform extracts were washed to neutrality, dried over anhydrous magnesium sulfate, combined, and evaporated to leave a residue of 5.864 g of crude reaction product. The mixture was purified by chromatography on 500 g of silica gel. The early benzene–ethyl acetate (9:1) eluates gave, after evaporation of the solvent, 3.383 g of a crystalline residue. The compound was recrystallized from acetone to yield a first crop of 1.917 g (34%), mp 247–249°, of the desired compound **5a**. A second crop amounted to 0.134 g, mp 238–243°.

An analytical sample had the following physical constants: mp 247–248°; $[\alpha]^{26}D$ +108° (*c* 1.106); $\lambda_{max}^{CH_3OH}$ 282 nm (ε 9600); $\bar{\nu}_{max}$ 3400, 1725, 1667, 1600 cm^{-1}; the nmr spectrum gave peaks at 387 (s) OH, 305 (m) 17α-H, 285 (m) 3β-H, 125 (s) and 120 (s) –OCOCH$_3$, 73 (s) and 65 (s) angular methyls.

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.36; H, 8.10.

3α,12β,17β-Triacetoxy-5β-androstan-11-one (3b). A. By-Product of the Above Oxidation.—Evaporation of the early benzene–ethyl acetate (4:1) eluates of the above chromatogram left 0.521 g of a solid. Several recrystallizations of this material from acetone–heptane led to the isolation of the triacetate **3b**, 0.156 g, mp 155–156°; $[\alpha]^{25}D$ +12° (*c* 0.994); $\bar{\nu}_{max}$ 1720 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; O, 24.97. Found: C, 66.89; H, 8.58; O, 24.73.

B. Acetylation of 3a.—The mixture of 0.325 g of the triolone **3a**, 6 ml of pyridine, and 6 ml of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was worked up as usual and the resulting crude acetylation product was recrystallized from acetone–heptane to yield 0.308 g of the desired triacetate **3b**, mp 155–156°, $[\alpha]^{24}D$ +11° (*c* 1.033), $\bar{\nu}_{max}$ 1720 cm^{-1}. Concentration of the mother liquors gave a second crop of 0.103 g, mp 154–155°. The first crop was given for analysis.

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.23; H, 7.99.

The by-product isolated from the oxidation mixture was identical in all regards with the sample prepared by acetylation of **3a**.

3α,17β-Diacetoxy-12β-hydroxy-5β-androstan-11-one (3c).—The later benzene–ethyl acetate (4:1) and the benzene–ethyl acetate (1:1) eluates of the above chromatogram of the oxidation mixture contained 0.673 g of substance. This material was recrystallized from acetone–heptane to yield 0.232 g of the diacetate **3c**, mp 189–190°. An analytical sample had the following physical constants: mp 189–190°; $[\alpha]^{25}D$ +52° (*c* 1.012); $\bar{\nu}_{max}$ 3465, 1721 cm^{-1}; $\bar{\nu}_{max}^{CCl_4}$ 3476 cm^{-1} (0.00125 *M*); the nmr spectrum showed peaks at 307 (m) 17α-H, 280 (m) 3β-H, 238 (d) 12α-H, 212 (d) 12β-OH, 123 (s) and 121 (s) –OCOCH$_3$, 72 (s) and 39 (s) angular methyls.

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.71; H, 8.31.

Acetylation of 0.110 g of the above compound **3c** gave 0.102 g of the triacetate **3b**, mp 154–155°, $\bar{\nu}_{max}$ 1720 cm^{-1}.

3α,11,17β-Triacetoxy-5β-androst-9(11)-en-12-one (5b).—Acetylation of 0.766 g of **5a** in 10 ml of pyridine and 5 ml of acetic anhydride led, after the usual work-up and recrystallization from acetone–heptane, to the isolation of a first crop of 0.579 g of **5b**, mp 188–189°; a second crop amounted to 0.163 g, mp 187–188°. An analytical sample had the following physical constants: mp 188–189°; $[\alpha]^{25}D$ +164° (*c* 1.102); $\lambda_{max}^{CH_3OH}$ 247 nm (ε 11,030) and 310 nm (ε 78); $\bar{\nu}_{max}$ 1750, 1720, 1694 cm^{-1}.

(40) J. S. McKechnie and I. C. Paul, *Experentia*, **23**, 612 (1967).

(41) The melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were determined with a Hilger and Watts polarimeter, and the infrared spectra were obtained with a Perkin-Elmer Model 421 grating spectrophotometer in chloroform solutions unless stated otherwise. The mass spectra were recorded on a MAT mass spectrometer Model CH 4.

(42) This experimental procedure was recommended by Dr. W. Cole of these laboratories.

(43) The residues of earlier eluates from the above column yielded two different compounds in small amounts, the analytical values of which were in agreement with the formula $C_{19}H_{30}O_4$. Since it was not known if these substances were ketols of the 13β-series or if epimerization at C_{13} had taken place, no structural assignment has yet been made.

Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.35; H, 7.98.

3α,17β-Diacetoxy-5β-androstan-11-one (4).—The general reduction procedure of Chapman[8] was followed. A solution of 0.750 g of the triacetate **3b** in 15 ml of toluene was added to a well-stirred solution of 0.840 g of freshly cut calcium lumps in about 100 ml of liquid ammonia. After a reaction time of 6 min the vigorously stirred mixture was treated with 3 ml of bromobenzene, then with 3 ml of water, and the ammonia was allowed to evaporate. The toluene was evaporated under reduced pressure on the steam bath and the residue was dissolved in 40 ml of methanol and 2 ml of water, 2 g of potassium hydroxide pellets was added, and the mixture was warmed to a gentle reflux for 45 min. The addition of 50 ml of water was followed by the evaporation of the methanol under reduced pressure. The remaining suspension was acidified with 2 *N* hydrochloric acid and the slurry was extracted with ether. The organic extract was washed to neutrality with water, dried, and evaporated to leave a residue of 0.586 g of crude reaction product. Acetylation of this material led to the isolation of 0.646 g of the crude reduced compound **4** which was purified by chromatography on 65 g of silica gel. From the benzene–ethyl acetate (19:1) eluates a residue of 0.442 g was obtained which was recrystallized once from ether–heptane to yield 0.417 g (68%) of pure 3α,17β-diacetoxy-5β-androstan-11-one (**4**), mp 180–181°.

A part of this sample was sublimed and recrystallized from ether–heptane for analysis: mp 180–181°; $[\alpha]^{25}D$ +52° (*c* 0.905 in acetone) [Sarett[9] reported mp 180–181°, $[\alpha]^{25}D$ +51.5° (*c* 0.9 in acetone)]; $\tilde{\nu}_{max}$ 1720, 1700 cm^{-1}; $\tilde{\nu}_{max}^{CS_2}$ 1733, 1709, 1024 cm^{-1}.[44]

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.94; H, 9.06.

3α,11α,17β-Trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic Acid 11a,17-Lactone (6a).—A mixture containing 3.173 g of 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (**5a**), 24.60 g of potassium hydroxide pellets, 570 ml of 1-propanol, and 55 ml of water was stirred in an atmosphere of nitrogen under a gentle reflux for 18 hr, essentially following the experimental procedure of Nace and Nelander.[13] The above solution was diluted with 700 ml of water and concentrated to 500 ml under reduced pressure. This procedure was repeated once. The resulting mixture was cooled and acidified with 900 ml of 2 *N* hydrochloric acid. The acidic solution was extracted with three successive 1000-ml portions of ether; the ether extracts were washed to neutrality with several 300-ml portions of water, dried over anhydrous magnesium sulfate, filtered, combined, and evaporated to leave 2.413 g of crude reaction product. This material was subjected to chromatographic purification on 280 g of silica gel. The benzene–ethyl acetate (1:1) eluates gave, after evaporation of the solvent and recrystallization of the residue from acetone–heptane, 1.915 g (76%) of the lactone **6a**, mp 187–188°.

An analytical sample of the compound had the following physical properties: mp 187–188°; $[\alpha]^{26}D$ −76° (*c* 1.011); no ultraviolet absorption at 282 nm; $\tilde{\nu}_{max}$ 3600, 1755 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.16; H, 8.67.

3α,11α-Diacetoxy-17β-hydroxy-13α-C-nor-5β-androstane-11β-carboxylic Acid 11a,17-Lactone (6b).—The above lactone **6a** (0.200 g) was acetylated in the usual manner in acetic anhydride and pyridine to yield, after work-up and recrystallization from acetone–heptane, 0.151 g of the pure diacetate **6b**, mp 179–180°. A second crop of 0.041 g, mp 175–178°, resulted from the concentrated mother liquors.

The first crop material had $[\alpha]^{26}D$ −82° (*c*, 1.044); $\tilde{\nu}_{max}$ 1770, 1730 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 68.29; H, 7.97. Found: C, 68.39; H, 7.80.

3α,11α,17β-Trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic Acid 11a,17-Lactone 3-*p*-Bromobenzoate (6c).—A mixture of 0.320 g of freshly distilled *p*-bromobenzoyl chloride, 0.320 g of the lactone **6a**, and 10 ml of pyridine was allowed to stand at room temperature for 4 hr. The reaction mixture was diluted with 250 ml of ether and 100 ml of water, the layers were separated, and the aqueous phase was extracted with two 150-ml portions of ether. The organic extracts were washed in sequence with three 75-ml portions of 2 *N* hydrochloric acid, 75 ml of water, three 75-ml portions of saturated sodium bicarbonate solution, and then to neutrality with three 75-ml portions of water. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a residue of 0.573 g of crude reaction product. Chromatographic purification of this material on 60 g of silica gel furnished in the eluates with benzene–ethyl acetate (19:1 and 9:1) the desired *p*-bromobenzoate **6c** which was recrystallized from acetone–heptane to furnish 0.271 g of an analytical sample: mp 250–251°; $[\alpha]^{22}D$ −34° (*c* 1.030); $\tilde{\nu}_{max}$ 3570, 1751, 1703 cm^{-1}; the nmr spectrum showed peaks at 472 (d) and 454 (d) (J_{AB} = 9 cps) aromatic H, 290 (m) 3β-H, 258 (m) 17α-H, 63 (s) and 68 (s) angular methyls.

Anal. Calcd for $C_{26}H_{31}BrO_5$: C, 62.03; H, 6.21. Found: C, 61.84; H, 6.20.

Concentration of the above mother liquors furnished a second crop of 0.151 g, mp 250–251°, and a third crop of 0.032 g, mp 245–251°.

11α,17β-Dihydroxy-3-oxo-13α-C-nor-5β-androstane-11β-carboxylic Acid 11a,17-Lactone (7a).—To the solution of 0.245 g of the lactone **6a** in 40 ml of acetone which was cooled to 5° there was added with swirling 0.8 ml of chromium trioxide reagent[14] in an atmosphere of nitrogen. After 15 min the reaction mixture was diluted with 660 ml of water, extracted first with 1000 ml of ether and then with two 600-ml portions of the same solvent, the ether extracts were washed to neutrality, dried, and evaporated to leave a residue of 0.233 g of oxidation product. The substance was recrystallized four times from acetone–heptane to yield 0.117 g of the pure ketone **7a**, mp 247–249°. A second crop amounted to 0.080 g, mp 242–244°.

The above first crop had $[\alpha]^{26}D$ −59° (*c* 1.014); $\tilde{\nu}_{max}$ 3578, 1755, 1700 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.83; H, 8.08.

11α-Acetoxy-17β-hydroxy-3-oxo-13α-C-nor-5β-androstane-11β-carboxylic Acid 11a,17-Lactone (7b).—The ketone **7a** prepared as described above (0.096 g) was acetylated in pyridine–acetic anhydride and the crude acetylation product was recrystallized four times from acetone–heptane to yield 0.050 g of analytically pure acetate **7b**: mp 176–178°; $[\alpha]^{26}D$ −97° (*c* 0.896); $\tilde{\nu}_{max}$ 1770, 1750 (sh), 1738, 1700 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.54; H, 7.89.

3α,11α,17β-Trihydroxy-13α-C-nor-5β-androstane-11β-carboxaldehyde 11a,17-Hemiacetal (8).—A solution of 0.960 g of 3α,11α,17β-trihydroxy-13α-C-nor-5β-androstane-11β-carboxylic acid 11a,17-lactone (**6a**) in 200 ml of anhydrous ether was added dropwise to a stirred suspension of 1.085 g of lithium aluminum hydride in 150 ml of anhydrous ether at room temperature. The mixture was stirred for 7 hr, allowed to stand at room temperature overnight, warmed to a gentle reflux for 10 min, and cooled. Moist ether (30 ml) was added gradually; this was followed by the addition of 5 ml of water and 100 ml of 2 *N* sulfuric acid. The layers were separated and the aqueous solution was extracted with two 250-ml portions of ether. The organic extracts were washed with water, saturated sodium bicarbonate solution, and again with water. The ether solutions were dried over anhydrous magnesium sulfate, filtered, combined, and evaporated to leave 1.060 g of an oily residue which no longer showed the lactone carbonyl absorption in the infrared spectrum.

The above product was subjected to chromatographic purification on 100 g of silica gel. From the benzene–ethyl acetate (1:1) eluates a total of 0.875 g of an oily residue was obtained after evaporation of the solvent. The compound could not be induced to crystallize. A typical chromatographic fraction contained in addition to the hemiacetal **8** one minor and two trace impurities as shown by thin layer chromatographic analysis (silica gel, benzene–methanol 4:1). The product **8** had $[\alpha]^{25}D$ −50° (*c* 1.014) and the infrared spectrum recorded in dilute carbon tetrachloride solutions (0.00125, 0.000625, and 0.000312 *M*) revealed absorptions at $\tilde{\nu}_{max}$ 3620 (free OH) and 3563 cm^{-1} (intramolecularly bonded OH).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.78; H, 9.38. Found: C, 70.44; H, 9.65.

17β-Formyloxy-3α-hydroxy-13α-C-nor-5β-androstan-11-one (9a).—A solution containing 0.875 g of the above hemiacetal **8** and 2.41 g of lead tetraacetate in 120 ml of glacial acetic acid

(44) This spectrum was recorded on a Perkin-Elmer infrared spectrophotometer, Model 21. The spectrum was found to be identical with spectrum No. 1711 of the "Collection of Documentation for Molecular Spectroscopy," Butterworths Scientific Publications, London, 1957.

was allowed to stand at room temperature overnight. The reaction mixture was diluted with 5 ml of ethylene glycol, allowed to stand for 5 min, and concentrated on the steam bath to about 20 ml. The mixture was taken up in 600 ml of ether and 200 ml of ice-cold water, the layers were separated, and the aqueous phase was extracted first with 600 ml of ether and then with 300 ml of ether. The organic extracts were washed with three 200-ml portions of water, three 200-ml portions of ice-cold saturated sodium bicarbonate solution, and again with water to neutrality. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to leave 0.835 g of an oily residue.

Chromatographic purification of this product on 100 g of silica gel gave rise to 0.739 g of the desired formate **9a** which was obtained in the eluates with benzene–ethyl acetate (4:1). The compound could not be obtained in crystalline form. A typical chromatographic fraction contained, in addition to the formate **9a**, three trace impurities as shown by thin layer chromatographic analysis (silica gel, benzene–methanol 9:1). The compound **9a** had $[\alpha]^{24}D$ −4° (*c* 0.972); ν_{max} 3605, 1720, 1170 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.92; H, 9.01.

3α,17β-Dihydroxy-13α-C-nor-5β-androstan-11-one (9b).—A solution of 0.729 g of the above-obtained product **9a** and 0.320 g of potassium carbonate in 25 ml of methanol and 3.5 ml of water was allowed to stand at room temperature for 5 days. The solution was diluted with 100 ml of distilled water and the methanol was removed under reduced pressure. The resulting crystalline suspension was cooled; the crystals were collected on a filter, washed with several small amounts of water, and dried to yield 0.466 g of compound. The turbid, aqueous filtrate was acidified with 2 *N* hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to leave 0.198 g of a solid residue. This material was shown to be identical with the above 0.466 g of product by infrared and nmr spectra and thin layer chromatography.

Chromatography of the above combined reaction product on 70 g of silica gel and two recrystallizations of the residues from the benzene–ethyl acetate (1:1) eluates from acetone–heptane gave rise to a first crop of 0.370 g of the desired C-nor ketone **9b**, of mp 184.5–185°. A second crop amounted to 0.156 g, mp 180–183°. The over-all yield of the ketone **9b** (both crops) from the lactone **6a** was 60%.

A part of the above first crop was recrystallized twice for analysis: mp 185–185.5°; $[\alpha]^{25}D$ +5° (*c* 1.01); ν_{max} 3600, 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.09, 73.90; H, 9.82, 9.66.

Registry No.—**2a**, 13976-62-0; **2b**, 13961-97-2; **3a**, 10437-34-0; **3b**, 13976-64-2; **3c**, 13976-65-3; **4**, 13976-66-4; **5a**, 10587-52-7; **5b**, 13976-68-6; **6a**, 10454-74-7; **6b**, 10454-75-8; **6c**, 13976-71-1; **7a**, 10454-76-9; **7b**, 10454-77-0; **8**, 13961-99-4; **9a**, 13962-00-0; **9b**, 13976-73-3; benzilic acid, 76-93-7.

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Selective Carbamylation with Methyl Isocyanate

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Reactions of methyl isocyanate ($CH_3N{=}C{=}O$), a fundamental decomposition product of some N-methylcarbamates, have been investigated. Nuclear magnetic resonance (nmr) was used to measure the end of the reaction in a sealed system. Reaction of $CH_3N{=}C{=}O$ with water proceeds slowly enough to be followed by nmr; no evidence was seen of large concentrations of CH_3ND_2 and CH_3NDCO_2D. Reaction of $CH_3N{=}C{=}O$ with 2-formylcyclohexanone, which can exist in three forms, yielded a fairly pure N-methylcarbamate. Nmr limited the derivation of the product to one of two possibilities. The *trans* structure was confirmed by reaction of $CH_3N{=}C{=}O$ with two other α-formyl ketones to yield a terminally substituted *trans* product; a small amount of pyridine was present, which may have shifted the equilibria. Reaction of $CH_3N{=}C{=}O$ with four aromatic ambident anions in pyridine at 100° yielded products indicating preferential attack on only one of the sites. 1,4-Naphthoquinone monoxime was carbamylated on the oxime to the exclusion of the ring products. The selective reaction of $CH_3N{=}C{=}O$ indicates that it has some steric requirements in the systems studied.

Many N-methylcarbamate esters of phenols, naphthols, ring hydroxylated heterocyclics, oximes, etc., act as insecticides probably by inhibiting esterases in a manner similar to the phosphate esters.[1,2] These carbamates are hydrolyzed to $CH_3N{=}C{=}O$ by various bases.[3,4] They are also pyrolyzed[5,6] and fragmented under electron impact[7] to yield $CH_3N{=}C{=}O$. Since $CH_3N{=}C{=}O$ appears to be a fundamental decomposition product of these carbamates, its reactions were further investigated in preparation for a study of the interaction of N-methylcarbamate insecticides with complex, living systems.

Although the reactivity of the —N=C=O group in general has been reviewed,[8,9] the reactions of $CH_3N{=}C{=}O$ are associated mainly with the insecticide literature.[1,2] In reported syntheses of N-methylcar-

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