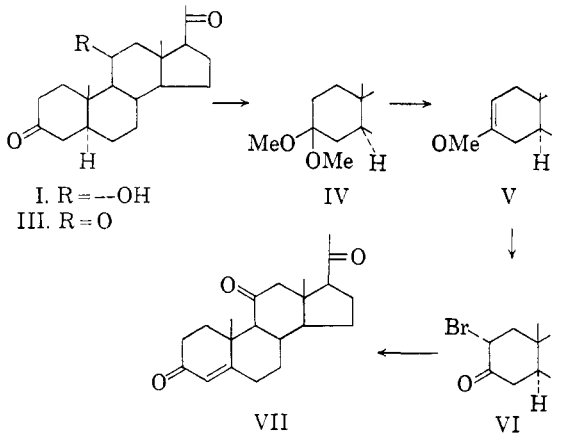
The Conversion of 5α-Pregnane-3,11,20-trione to 11-Ketoprogesterone

BARNEY J. MAGERLEIN

Received March 17, 1959

The initial step in one of the early methods for the synthesis of cortisone from 11α-hydroxyprogesterone[1] was the catalytic reduction of the Δ^4-double bond.[2] The reduction of 11α-hydroxyprogesterone gives predominantly the 5β (normal) dihydroisomer, but the 5α (allo) isomer I is isolated in yields up to 30%.[2] 11α-Hydroxy-5α-pregnane-3,20-trione (I) may be converted to cortisone acetate *via* 21-acetoxy-17α,21-dihydroxy-5α-pregnane-3,11,20-trione (II) (allo dihydrocortisone acetate). The difficulty of the introduction of the Δ^4-double bond into allo dihydrocortisone acetate is well known.[3]

This note describes the conversion of 11α-hydroxy-5α-pregnane-3,20-dione (I) to the versatile intermediate, 11-ketoprogesterone (VII).[4] 11α-Hydroxy-5α-pregnane-3,20-dione (I) was oxidized with chromic acid to the allo trione III. The 3-



methyl ketal was selectively prepared in 44% yield using selenium dioxide in methanol.[5] Pyrolysis of the ketal IV formed the enol ether to which the structure V is assigned. When V was treated with hypobromous acid[6] the 2-bromide VI was formed in almost quantitative yield. The infrared spectrum of VI showed raised carbonyl absorption at 1720 cm.$^{-1}$ as well as the usual carbonyl absorption at 1700 cm.$^{-1}$ The displacement of the carbonyl to the higher frequency is indicative of 2-equatorial or 2α-bromine.[7] Dehydrohalogenation of the 2-bromide using lithium chloride-dimethyl formamide[8] gave 11-ketoprogesterone in 40% yield. Less than 5% yield of the Δ^1-isomer was detected in the crude dehydrohalogenation product.[9]

EXPERIMENTAL[10]

3,3-Dimethoxy-5α-pregnane-11,20-dione (IV). A mixture of 20 g. of 5α-pregnane-3,11,20-trione, 20 g. of selenium dioxide, and 500 ml. of methanol was stirred at room temperature for 2 days. The mixture was filtered and poured into 2 l. of water containing sufficient sodium hydroxide to make the solution alkaline. Extraction of the aqueous mixture with methylene chloride gave a crystalline residue which when recrystallized from methanol yielded 10 g. of IV, m.p. 130–136°. The yield was 43.8%. Several recrystallizations from methanol gave material melting at 148–151°, $[\alpha]_D$ +104° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.61; H, 9.80.

3-Methoxy-5α-2-pregnene-11,20-dione (V). Five g. of IV, m.p. 130–136°, was heated at 220° until bubbling ceased. About 9 min. was required. The cooled melt was crystallized from methanol to give 2.58 g. of V, m.p. 154–156°. The yield was 56.4%. Recrystallization yielded broad melting products of inferior quality. The crude reaction product was therefore not purified but used directly in the next step.

2α-Bromo-5α-pregnane-3,11,20-trione (VI). A solution of 564 mg. of *N*-bromosuccinimide in 30 ml. of *t*-butyl alcohol and 20 ml. of 0.8*N* sulfuric acid was added to a solution of 1.0 g. of enol ether V in 25 ml. of *t*-butyl alcohol. After 2 min. the reaction mixture was poured into water. The crystals were filtered and dried. The yield of VI, m.p. 167–173°, was 1.10 g. (93.4%). Recrystallization from methanol raised the m.p. to 170–172.5°, $[\alpha]_D$ +144° (acetone), λ_{max}^{Nujol} 1720, 1700, 709 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.41; H, 7.13; Br, 19.47, 19.43.

11-Ketoprogesterone (VII). A solution of 1.04 g. of bromide VI, 300 mg. of lithium chloride, and 3 ml. of dimethylformamide was heated under nitrogen at 70–80° for 2 hr. The cooled mixture was diluted with 10 ml. of water and 10 ml. of saturated sodium chloride solution. The crystalline product weighed 810 mg. (97.4%). Recrystallization from methanol afforded 340 mg. (40.8%) of VII, m.p. 164–168°. Pure 11-ketoprogesterone, (260 mg., 31.2%) m.p. 170.5–172.3°, $[\alpha]_D$ +265° ($CHCl_3$), (λ_{max}^{EtOH} 239 mμ, a_M 15,500)

(1) D. H. Peterson and H. C. Murray, *J. Am. Chem. Soc.*, **74**, 1871 (1952).

(2) O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

(3) (a) G. Rosenkranz, C. Djerassi, R. Yashin, and J. Pataki, *Nature*, **168**, 28 (1951); (b) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **74**, 2248 (1952); (c) R. M. Evans, J. C. Hamlet, T. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walter, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(4) See for example J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

(5) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6113 (1954).

(6) B. J. Magerlein, D. A. Lyttle, and R. H. Levin, *J. Org. Chem.*, **20**, 1709 (1955).

(7) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953).

(8) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(9) See J. J. Beerboom and C. J. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954) who reported that dehydrohalogenation of 4α-chlorocholestanone afforded a mixture from which Δ^1- and Δ^4-Cholesten-3-one were isolated in yields of 43 and 31%, respectively.

(10) The author is indebted to W. A. Struck and associates for the elemental analyses, to Mrs. G. S. Fonken for the infrared data, and to L. M. Reineke and associates for paper chromatography analyses.

was obtained by a final recrystallization from methanol. The infrared curve of this material was identical with that of pure 11-ketoprogesterone. Paper chromatography of the crude reaction product showed the presence of less than 5% of 1-dehydro-5α-pregnane-3,11,20-trione.

RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICH.

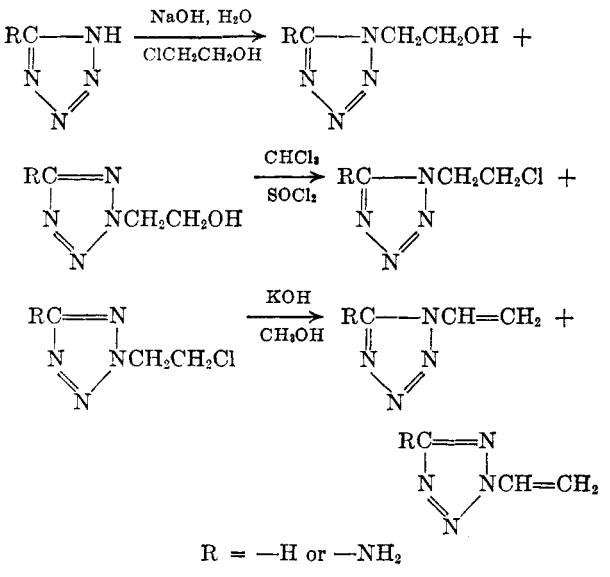
N-Vinyltetrazoles

WILLIAM G. FINNEGAN AND RONALD A. HENRY

Received March 18, 1959

As part of a continuing program on the synthesis of new *N*-alkyl substituted tetrazoles,[1] the syntheses and polymerizations of the *N*-vinyltetrazoles, their 5-amino derivatives, and the *N*-allyltetrazoles were investigated.

The following sequence of reactions was employed for the syntheses of the *N*-vinyltetrazoles:



When tetrazole was employed as the starting material, the sequence of reactions was carried out as indicated and the 1- and 2-vinyltetrazoles were separated by distillation at reduced pressure. With 5-aminotetrazole, it was convenient to separate the isomers by crystallization at the hydroxyethyl stage[1] and convert these to the vinyl derivatives independently.

1- and 2-Allyltetrazoles were readily synthesized in moderate yields by direct alkylation of sodium tetrazole with allyl bromide in refluxing aqueous ethanol solution.

No attempts were made to bring the syntheses of the vinyl derivatives to optimum yields. It is anticipated, however, that vinylation with acetylene[2] would be the preferred approach.

In preliminary polymerization studies, the vinyltetrazoles and the vinyl-5-aminotetrazoles gave only insoluble-infusible homopolymers, regardless of whether solution or emulsion techniques were employed. The possibility of di-vinyl derivatives of tetrazole as impurities appears to be remote since di-*N*-alkylation of the tetrazole ring results in the formation of undistillable tetrazolium salts.[3] The insolubility of the vinyltetrazole polymers must be due either to strong molecular interactions between polymer chains, to ring involvement during free radical propagation, or possibly to involvement of the proton in the 5-position in the case of the 1- and 2-vinyltetrazoles. Limited attempts using chain transfer agents in solution polymerizations were more successful; initially soluble polymers were obtained with 1- and 2-vinyltetrazoles, but re-solution of the freshly precipitated and undried polymers gave solutions which jelled in a short time. The 1- and 2-allyltetrazoles could not be induced to homopolymerize, but would copolymerize with styrene and methyl methacrylate.[4]

Refractive indices and densities were measured and the molar refractivity of the tetrazole ring was calculated for each of the liquid tetrazoles. These data are shown in Table I.

TABLE I

INDICES AND DENSITIES OF LIQUID TETRAZOLES

Tetrazole	η_D^t	D_4^t	M_k Tetrazole Ring
1-Ethyltetrazole[a]	1.4602^{25}	1.12^{25}	12.7
2-Ethyltetrazole[a]	1.4366^{25}	1.07^{25}	12.7
1-Allyltetrazole	1.4854^{20}	1.12^{20}	12.6
2-Allyltetrazole	1.4670^{20}	1.08^{20}	12.7
1-Vinyltetrazole	1.5000^{20}	1.18^{20}	13.1
2-Vinyltetrazole	1.4850^{20}	1.13^{20}	13.4

[a] Synthesized for comparison by the method used for the syntheses of 1- and 2-allyltetrazoles. *Cf.* ref. (9) for physical constants.

EXPERIMENTAL[5]

Tetrazole. Tetrazole was prepared by diazotization of 5-aminotetrazole in the presence of hypophosphorous acid.[6] An improvement was made in the procedure[7] by extracting the tetrazole with ethyl acetate directly from the reaction

(1) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 76, 923 (1954).

(2) J. W. Copenhaver and M. H. Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold Publishing Corp., New York, N. Y., 1949, p. 66.

(3) G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chemistry and Industry*, 42, 1355 (1955).

(4) Charles J. Thelen, this laboratory, unpublished results.

(5) The melting points were determined in capillary tubes and are uncorrected.

(6) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 76, 290 (1954).

(7) This improvement is a variation of one suggested by James Moffat, University of Louisville, Louisville, Ky.