

75 ml. of a water suspension of phenyl- β -naphthylamine and was coagulated with salt-dilute acid solution, washed with tap water, and dried overnight at 70°.

The results of some typical runs are listed in Table II.

The polymers obtained were essentially gel-free even though no modifier was used. No microgel was detected by centrifuging or by cold-milling.

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The Mechanism of Elimination of Hydrogen Bromide from α -Bromo Ketosteroids through Formation of Hydrazones

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Recently a reaction has been described in which the atom of bromine in 4-bromo-3-ketosteroids was removed as hydrogen bromide with the introduction of a double bond at C₄-C₅ as a sequel to formation of the 3-(2,4-dinitrophenylhydrazone).¹ Discussion of the mechanism of the reaction was limited to the statement that "the reactivity of the bromine at C₄ is greatly increased through formation of a hydrazone at C₃."

Djerassi has extended the reaction to other 3-keto α -bromo steroids and has suggested a mechanism² for the elimination of hydrogen bromide and the formation of an unsaturated hydrazone in acetic acid.

We wish to report some additional observations on the reaction of hydrazines with α -bromo-ketosteroids, and to suggest that the mechanism for the activation of the atom of bromine and the subsequent reactions which occur is as follows: (1) the hydrazone I is formed with the atom of bromine still intact, (2) an attack of the solvent on the bromine occurs and electrons are donated by the atom of nitrogen alpha to the phenyl group to form a resonance hybrid to which structures II and the carbonium ion III contribute, and (3) the carbonium ion is stabilized either through loss of a proton and formation of a double bond to give IV or through the addition of a negative group to give the C₄ substituent V. This mechanism correlates the reactivity of the halogen atom in I with that of other compounds³ in which the halogen atom is alpha to a double bond or conjugated system that can act as an electron donor.

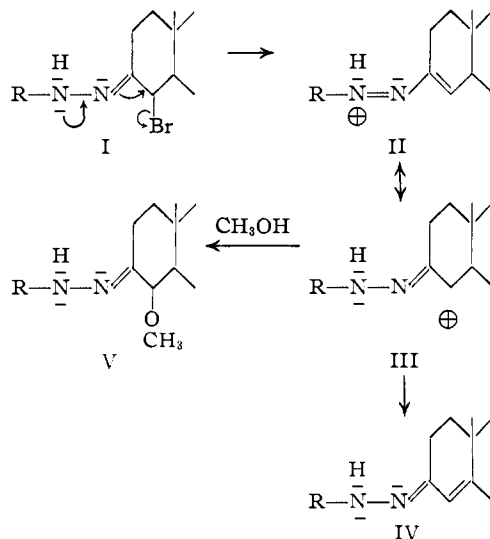
The essential difference between this mechanism and the one suggested by Djerassi is that (1) the bromine is not lost until after the hydrazone is formed, and therefore a hydroxy imino structure is not involved, and (2) with the hydrazone grouping as an intermediate the atom of nitrogen alpha to the phenyl group is the principal donor of electrons.

Hydrogen bonding between the atom of nitrogen alpha to the phenyl group and the bromine

(1) Mattox and Kendall, *THIS JOURNAL*, **70**, 882 (1948).

(2) Djerassi, *ibid.*, **71**, 1003 (1949).

(3) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).



appears not to be essential, for α,α -diphenylhydrazine removes hydrogen bromide from 4-bromo-3-ketosteroids. However, with the diphenylhydrazine, structure I could be formed as with mono substituted hydrazines. With disubstituted hydrazines and 2-bromo-3-ketosteroids, Djerassi² has obtained similar results.

The formation of an unsaturated hydrazone with loss of hydrogen chloride from a chloroaldehyde by treatment with 2,4-dichlorophenylhydrazine has been reported by Chattaway and Irving.⁴ van Alphen⁵ has clarified earlier investigations⁶ concerned with the removal of hydrogen chloride from chloroacetoacetic ester with phenylhydrazine. In this instance an azo compound is formed. It appears probable that a structure analogous to I is an intermediate, but since an atom of hydrogen beta to the ketone is not available a proton is lost from the atom of nitrogen alpha to the phenyl group. van Alphen⁷ also showed that phenacyl chloride in ethanol lost hydrogen chloride when treated with phenylhydrazine to yield [1,3-diphenyl-(1,2-diazacyclobutene-2)]. Djerassi,⁸ on the other hand, observed that 2,4-dinitrophenylhydrazine did not remove hydrogen bromide from phenacyl bromide.

When semicarbazide was added to an acetic acid solution of methyl 3,11-diketo-4,12-(α)-dibromocholanate, a yellow color developed rapidly and faded within an hour or two to give a colorless semicarbazone of the Δ^4 -steroid. When methanol was used as the solvent, the semicarbazone of the 4-methoxy steroid⁹ was ob-

(4) Chattaway and Irving, *J. Chem. Soc.*, 88 (1930).

(5) van Alphen, *Rec. trav. chim.*, **64**, 109 (1945); **64**, 305 (1945).

(6) Bender, *Ber.*, **20**, 2747 (1887); Freer, *Am. Chem. J.*, **21**, 14 (1899).

(7) van Alphen, *Rec. trav. chim.*, **65**, 112 (1946).

(8) Personal communication.

(9) The structure of this compound was shown by conversion with pyruvic acid to methyl 3,11-diketo-4-methoxy-12(α)-bromocholanate: unpublished work.

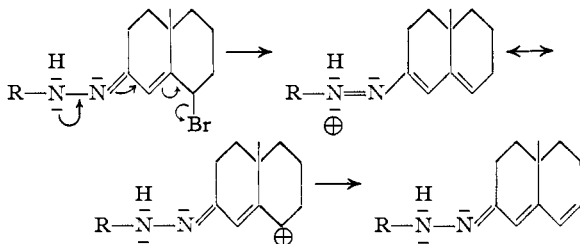
tained. The formation of the 4-methoxy semicarbazone is interpreted as the addition of a methoxyl group to the carbonium ion formed at C₄ by dissociation of the atom of bromine.

When methyl 3,11-diketo-4,12(α)-dibromochol-
anate is treated with 2,4-dinitrophenylhydrazine in acetic acid, hydrogen bromide is eliminated and the corresponding 2,4-dinitrophenylhydrazone of the Δ⁴-steroid can be obtained in excellent yield.¹ However, in methanol a mixture is obtained which can be separated into the Δ⁴-cholenate hydrazone and the 4-methoxy hydrazone.⁹ This is another example of substitution at C₄, instead of elimination of hydrogen bromide.

The 3-(2,4-dinitrophenylhydrazone) of methyl 3,11-diketo-12(α)-bromochol-
anate can be brominated in chloroform to yield the bromo hydrazone, which is stable in this solvent. When the chloroform is displaced with acetic acid-acetic anhydride (2:1) there is a rapid loss of hydrogen bromide to give the hydrazone of the Δ⁴-steroid. The position of the double bond, together with the maximum absorption of light at 364 mμ indicate that the position of the atom of Br was at C₄.

This experiment in which the hydrazone of the steroid was formed before introduction of the bromine at C₄ can be explained by Djerassi's hypothesis² only on the assumption that the hydrazone was hydrated before elimination of hydrogen bromide. This seems quite improbable under the conditions used.

Djerassi² has shown that hydrogen bromide is eliminated from a 6-bromo-3-keto-Δ⁴-steroid by treatment with 2,4-dinitrophenylhydrazine, and has discussed a mechanism for the reaction. It is evident that the mechanism suggested in the present note can be extended to apply to the elimination process. Finally, it is probable that



treatment of the 6-bromo-3-keto-Δ⁴-steroid with 2,4-dinitrophenylhydrazine under other conditions would lead to substitution of a negative group at C₆ instead of formation of a double bond at C₆-C₇.

Experimental

Methyl 3,11-Diketo-12(α)-bromo-Δ⁴-cholenate-3-semicarbazone.—The semicarbazone was prepared with 1.120 g. of methyl 3,11-diketo-4,12(α)-dibromochol-
anate, 448 mg. of semicarbazide hydrochloride and 410 mg. of sodium acetate in 30 ml. of acetic acid on the steam-bath. After thirty minutes the solution was cooled, diluted with water and extracted with chloroform. The aqueous phase contained 97% of the theoretical amount of bromide ion. The chloroform was removed under reduced pressure and the residue was crystallized from methanol; yield, 488

mg., m. p. 206–211°. After several crystallizations from methanol the product melted at 213–215° (dec.). It did not depress the melting point of the semicarbazone prepared from the corresponding 3-keto-Δ⁴ compound; [α]_D +15 ± 2° (32.0 mg. in 3.00 ml. chloroform); λ_{max}^{methanol} 269 mμ; ε 29,700.

Anal. Calcd. for C₂₈H₃₈O₄N₃Br: C, 58.20; H, 7.14. Found: C, 58.16; H, 7.07.

The semicarbazone of methyl 3,11-diketo-12(α)-bromo-Δ⁴-cholenate was prepared from the 3-keto-Δ⁴ compound in aqueous methanol, and was crystallized from aqueous methanol: elongated hexagonal plates, m. p. 209–210° (dec.); λ_{max}^{methanol} 269 mμ; ε 32,200.

**Methyl 3,11-Diketo-4-methoxy-12(α)-bromochol-
anate-3-semicarbazone.**—A solution of 448 mg. of semicarbazide hydrochloride and 328 mg. of sodium acetate in 16 ml. of water was added to 1.120 g. of methyl 3,11-diketo-4,12(α)-dibromochol-
anate in 160 ml. of methanol. After two hours at room temperature water was added, the methanol was removed under reduced pressure and the residue was distributed between chloroform and water. The aqueous phase contained 100% of the theoretical amount of halogen for quantitative removal of the hydrogen bromide. The chloroform was removed under reduced pressure, and the residue was crystallized from methanol; yield, 682 mg., m. p. 208–209° (dec.); 278 mg., m. p. 190–200° (dec.). After several crystallizations from chloroform-methanol a product which melted at 215–216° was obtained; [α]_D +17 ± 2° (29.2 mg. in 3.00 ml. CHCl₃); λ_{max}^{methanol} 230 mμ; ε 13,600.

Anal. Calcd. for C₂₇H₄₀O₅BrN₃: C, 57.03; H, 7.45; CH₃O, 10.92. Found: C, 57.31; H, 7.75; CH₃O, 11.35.

**Methyl 3,11-Diketo-4-methoxy-12(α)-bromochol-
anate-3-(2,4-dinitrophenylhydrazone) and Methyl 3,11-Diketo-12(α)-bromo-Δ⁴-cholenate-3-(2,4-dinitrophenylhydrazone).**—To 238 mg. of 2,4-dinitrophenylhydrazine dissolved in 125 ml. of methanol was added 560 mg. of methyl 3,11-diketo-4,12(α)-dibromochol-
anate at room temperature. The air in the flask was displaced with carbon dioxide and after twenty-four hours the solution was filtered. The hydrazone weighed 622 mg. The mother liquor contained the theoretical amount of bromide ion.

The 622 mg. of crystalline material was dissolved in benzene-petroleum ether (1:1) and absorbed on a column of 20 g. of magnesium silicate-infusorial earth (1:1). The column was eluted with increasing concentrations of benzene in petroleum ether, and finally with benzene alone.

A yellow hydrazone, eluted first, weighed 419 mg. (61%). Crystallization from chloroform-methanol gave 340 mg. of yellow needles, m. p. 234–235°. After several recrystallizations the product melted at 240–241°; λ_{max}^{chloroform} 370 mμ, ε 26,500.

Anal. Calcd. for C₃₂H₄₈O₈N₄Br: C, 55.57; H, 6.27; CH₃O, 8.97. Found: C, 55.48; H, 6.16; CH₃O, 9.06.

The hydrazone remaining on the column was eluted with benzene containing 1% methanol and crystallized twice from chloroform-acetic acid. The red product (86 mg.) melted at 242–243°, and did not depress the melting point of methyl 3,11-diketo-12(α)-bromo-Δ⁴-cholenate-3-(2,4-dinitrophenylhydrazone); λ_{max}^{chloroform} 387 mμ, ε 30,000.

**Methyl 3,11-Diketo-12(α)-bromochol-
anate-3-(2,4-dinitrophenylhydrazone).**—A solution of 2.40 g. of 2,4-dinitrophenylhydrazine in 325 ml. of acetic acid was added to 4.81 g. of methyl 3,11-diketo-12(α)-bromochol-
anate in 75 ml. of acetic acid at room temperature. After one hour the hydrazone was precipitated with water and recrystallized several times from ethyl acetate-methanol. The yellow crystals melted at 190–191°; λ_{max}^{chloroform} 367 mμ; ε 25,000.

Anal. Calcd. for C₃₁H₄₁O₇N₄Br: C, 56.27; H, 6.25. Found: C, 56.28; H, 6.32.

**Bromination of Methyl 3,11-Diketo-12(α)-bromochol-
anate-3-(2,4-dinitrophenylhydrazone).**—One millimole of methyl 3,11-diketo-12(α)-bromochol-
anate-3-(2,4-dinitrophenylhydrazone) was treated with 1.0 ml. of bromine in 10 ml. of chloroform. The solution was allowed to stand in the dark for 24 hours. The chloroform was removed under reduced pressure and the residue was crystallized from methanol; yield, 488

phenylhydrazine) in 100 ml. of dry chloroform was brominated with 2.00 ml. of 1.02 *N* bromine in chloroform. After two minutes water was added. The aqueous phase contained 10.7 ml. of 0.10 *N* Br⁻. A second wash with water after five minutes contained 0.3 ml. of 0.10 *N* Br⁻. The chloroform phase was filtered through a pad of anhydrous sodium sulfate; $\lambda_{\text{max}}^{\text{chloroform}}$ 364 m μ ; ϵ 23,600.

Methyl 3,11-Diketo-12(α)-bromo- Δ^4 -cholenate-3-(2,4-dinitrophenylhydrazine).—Chloroform was removed under reduced pressure from a half of the solution. The residue was dissolved in 10 ml. of acetic acid and 5 ml. of acetic anhydride under carbon dioxide. Red crystals which separated within five minutes were filtered after three hours. This material (276 mg., 84% yield; m. p. 237–239°) was identical with a sample of the Δ^4 -hydrazine. Admixture with this sample did not depress the melting point; $\lambda_{\text{max}}^{\text{chloroform}}$ 387 m μ ; ϵ 30,200.

Chloroform was removed from the remaining half of the solution and the residue was dissolved in 15 ml. of acetic acid under carbon dioxide. Yellow crystals which separated after twelve minutes were filtered after three hours. The material weighed 298 mg. and was a mixture of the Δ^4 -hydrazine and its hydrobromide salt; $\lambda_{\text{max}}^{\text{chloroform}}$ 387 m μ ; $E_{1\text{cm}}^{1\%}$ 402. Eighty-three per cent. of the theoretical amount of hydrogen bromide was present in the aqueous phase after distribution of 71 mg. of the crystals between water and chloroform. From the organic phase, after displacement with acetic acid, red crystals (43 mg., m. p. 237–238°) of the Δ^4 -hydrazine were separated. Admixture with a sample of this hydrazine did not depress its melting point; $\lambda_{\text{max}}^{\text{chloroform}}$ 387 m μ ; ϵ 30,100.

This hydrobromide was also prepared from 264 mg. of the Δ^4 -hydrazine in 1.60 ml. of chloroform with 0.40 ml. of 2.08 *N* hydrobromic acid in acetic acid and 16 ml. of acetic acid. After fifteen minutes the yellow crystals were filtered under carbon dioxide and placed in a vacuum desiccator over sodium hydroxide. The wet crystals turn red if exposed to moisture. After drying, the yellow crystals (140 mg.) became red when heated to 130° and melted at 241–242°; $\lambda_{\text{max}}^{\text{chloroform}}$ 387 m μ ; $E_{1\text{cm}}^{1\%}$ 417. After distribution between chloroform and water, the aqueous phase contained 85% of the theoretical amount of hydrogen bromide.

Methyl 3,11-Diketo-4,12(α)-dibromocholanate-3(2,4-dinitrophenylhydrazine).—Bromination of 2 millimoles of methyl 3,11-diketo-12(α)-bromocholanate-3(2,4-dinitrophenylhydrazine) was carried out as described. The chloroform was removed under reduced pressure to 10 ml., and 120 ml. of absolute ether was added. Canary yellow crystals separated, and three further crops were obtained by concentration of the mother liquor and the addition of ether. The total yield was 80%. An analytic sample was prepared by recrystallization of the first crop from chloroform-ether. When heated, the yellow crystals became red and melted at 134–137°; $\lambda_{\text{max}}^{\text{chloroform}}$ 364 m μ , ϵ = 24,500. Calcd. for C₃₁H₄₀O₇N₄Br: C, 50.28; H, 5.45; Br, 21.59. Found: C, 50.07; H, 5.57; Br, 21.64; $[\alpha]_D$ -169 \pm 2° (29.6 mg. in 3 ml. CHCl₃).

With another sample $[\alpha]_D$ -181 \pm 2° (31.5 mg. in 3 ml. CHCl₃). After four hours and forty-five minutes this solution had become red, $[\alpha]_D$ -113 \pm 2°. This indicates loss of hydrogen bromide in the chloroform solution.

The crystals of the 4-bromohydrazine were converted into the Δ^4 -hydrazine in two ways. A. The bromohydrazine (148 mg.) was dissolved in 20 ml. of acetic acid at room temperature in an atmosphere of carbon dioxide. The yellow hydrobromide of the Δ^4 -hydrazine separated after ninety minutes. The hydrogen bromide was removed by solution of the crystals in acetic acid and chloroform and concentration of the solvents under reduced pressure. The red Δ^4 -hydrazine separated in 80% yield; m. p. 238–239°; $\lambda_{\text{max}}^{\text{chloroform}}$ 387 m μ ; ϵ = 29,400. B. One hundred ten milligrams of bromohydrazine was dissolved in 5 ml. of acetic anhydride and 10 ml. of acetic acid at room temperature in an atmosphere of carbon dioxide. After three hours the solution was concentrated under reduced pressure and the red Δ^4 -hydrazine was ob-

tained in 85% yield; m. p. 238–239°, $\lambda_{\text{max}}^{\text{chloroform}}$ 388 m μ , ϵ = 30,900.

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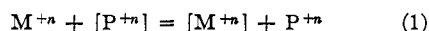
Cation Exchange Equilibria at Constant Ionic Strength

BY STANLEY W. MAYER

The theory of cation exchange equilibria has been developed to the stage at which activity quotient relationships have been formulated.¹ Unfortunately, serious uncertainty with regard to the mixed electrolyte activity coefficients in the resin, as well as in the aqueous phase,² has negated attempts to develop simple formulations for the equilibrium concentrations of the electrolytes in both phases.

Extensive investigations have shown that very frequently,³ in a mixture of electrolytes at constant total ionic strength, the logarithm of the activity coefficient of an electrolyte varies linearly with its ionic strength, even when the solvent is a mixture of organic and inorganic molecules. When the ions involved in an exchange are of equal charge, the total ionic strength remains constant. For such exchanges, the principle of linear variation has been empirically applied in this note to develop a simple relationship for the equilibrium concentrations in both phases.

The exchange between two ions of equal charge, *n*, can be written as



where the bracket signifies that the ion is in the resin phase. Following the development of Connick and Mayer²

$$K = \frac{m_{[M^{+n}]} m_{P^{+n}} \gamma_{[M^{+n}]} \gamma_{P^{+n}} \gamma_{[X^-]}^n \gamma_{X^-}^n}{m_{M^{+n}} m_{[P^{+n}]} \gamma_{M^{+n}} \gamma_{[P^{+n}]} \gamma_{X^-}^n \gamma_{X^-}^n} \quad (2)$$

$$K_m = K \frac{\gamma_{MX_n}^{n+1} \gamma_{PX_n}^{n+1}}{\gamma_{M^{+n}}^{n+1} \gamma_{P^{+n}}^{n+1}} \quad (3)$$

where K_m is the concentration quotient $m_{[M^{+n}]} / m_{P^{+n}} / m_{M^{+n}} m_{[P^{+n}]}$.

$$\log K_m = \log K + (n+1) (\log \gamma_{\neq 1} + \log \gamma_{\neq 2}) - \log \gamma_{\neq 1} - \log \gamma_{\neq 2} \quad (4)$$

where electrolyte 1 is MX_n, electrolyte 2 is PX_n.

For those electrolytes which follow the law of linear variation at constant total ionic strength (employing the notation of Harned and Owen,³ p. 459)

$$\log \gamma_{\neq 1} = \log \gamma_{(0)1} + \alpha_{12} \mu_1 \quad (5)$$

$$\log \gamma_{\neq 2} = \log \gamma_{(2)0} - \alpha_{21} \mu_{[1]} \quad (6)$$

$$-\log \gamma_{\neq 1} = -\log \gamma_{(0)1} - \alpha_{[12]} \mu_{[1]} \quad (7)$$

$$-\log \gamma_{\neq 2} = -\log \gamma_{(2)0} + \alpha_{21} \mu_1 \quad (8)$$

(1) Boyd, Schubert and Adamson, *THIS JOURNAL*, **69**, 2836 (1947).

(2) Connick and Mayer, *ibid.*, to be published.

(3) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1943, p. 454 ff.