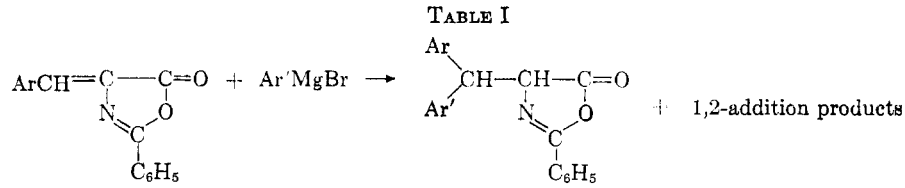
TABLE I



Ar	Ar'	% Yield of 1,4-addition product	% Yield of 1,2-addition product	M.p.[a] of 1,4-addition product, °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	C_6H_5	65	2	...	...	...	...	...	...
C_6H_5	o-$CH_3C_6H_4$	62	3	...	...	...	...	...	...
C_6H_5	p-$CH_3C_6H_4$	25	30	...	...	...	...	...	...
C_6H_5	p-ClC_6H_4	75	1	...	...	...	...	...	...
C_6H_5	o-ClC_6H_4	50	2	...	...	...	...	...	...
C_6H_5	o-$CH_3OC_6H_4$	40	20	...	...	...	...	...	...
C_6H_5	p-$CH_3OC_6H_4$	38	40	...	...	...	...	...	...
C_6H_5	1-$C_{10}H_7$	40	19	205	...	...	...	...	...
p-$CH_3OC_6H_4$	C_6H_5	64	2	...	...	...	...	...	...
o-ClC_6H_4	C_6H_5	64	3	...	...	...	...	...	...
p-ClC_6H_4	C_6H_5	63	0	...	...	...	...	...	...
1-$C_{10}H_7$	C_6H_5	60	0	205	$C_{26}H_{19}NO_2$	82.74	82.96	5.07	5.04
2-$C_{10}H_7$	C_6H_5	62	0	105	$C_{26}H_{19}NO_2$	82.74	82.98	5.07	5.07
p-$CH_3C_6H_4$	C_6H_5	64	0	145	...	...	...	...	...
m-$CH_3C_6H_4$	C_6H_5	60	0	158	$C_{23}H_{19}NO_2$	81.15	80.93	5.63	5.43
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	40	10	189	$C_{24}H_{21}NO_4$	74.40	73.90	5.46	5.50
p-$CH_3OC_6H_4$	p-ClC_6H_4	60	0	170	$C_{23}H_{18}NO_3Cl$	70.65	70.30	4.63	4.52
o-ClC_6H_4	p-ClC_6H_4	60	0	149	$C_{22}H_{15}NO_2Cl_2$	66.67	67.09	3.82	4.01

[a] The compounds whose melting points and analyses have not been reported here were identical with samples reported in references 1, 4, and 6.

The reaction mixture was refluxed in a nitrogen atmosphere. A grey powder was obtained.[11] On standing in air, copper metal and biphenyl, m.p. 72°, were obtained. The copper dissolved in concentrated nitric acid to give reddish brown fumes of nitrogen dioxide and a blue solution of cupric nitrate.

Reaction of I with Phenylcopper and Phenylmagnesium Bromide.—To a suspension of phenylcopper,[11] prepared in a nitrogen atmosphere, from 0.9 g. of magnesium, 8.17 g. of iodobenzene, and 7.2 g. of cuprous iodide, was added a solution of phenylmagnesium bromide, prepared from 0.6 g. of magnesium and 2.7 ml. of bromobenzene. A suspension of I (6.25 g.) in 250 ml. of ether was added in portions over a period of 1 hr. The mixture was refluxed for an additional 2 hr. and decomposed with a saturated solution of ammonium chloride. The ether layer gave 5.3 g. of 2 phenyl-4-benzhydryl-5-oxazolone, m.p. 159°, and 0.25 g. of compound II.

Reaction of I with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride.—To a solution of phenylmagnesium bromide, prepared from 0.9 g. of magnesium and 3.95 ml. of bromobenzene, was added 3.13 g. of I, suspended in ether, during a 1-hr. period. Anhydrous cobaltous chloride (2.23 g.) was added at the same time. The reaction mixture was heated under reflux for 2 hr. and decomposed with a saturated solution of ammonium chloride. The ether layer was separated, the residue dissolved in dilute hydrochloric acid (1:1), and the hydrochloric acid layer extracted with ether. The combined ether layers were washed with water and dried over anhydrous magnesium sulfate. The ethereal layer gave 0.80 g. of the saturated azlactone (20% yield), 0.5 g. of biphenyl, and 1.7 g. of α-benzamidobenzalacetophenone (V) (40%). These compounds were separated by fractional crystallization from ethanol and benzene. Compound V gave no melting point depression when mixed with an authentic sample.[5]

Spectral Measurements and Analyses.—Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer, using chloroform or methylene chloride as solvent. Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Illinois.

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A Selective Oxidation of Δ^5-3β-Hydroxy Steroids to Δ^4-3-Keto Steroids *via* 5α,6β-Dichloro Intermediates

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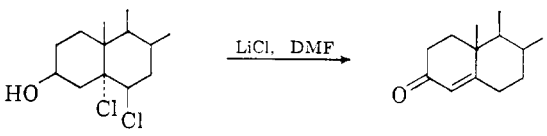
In connection with another project there was occasion to treat a 3β-hydroxy-5α,6β-dichloro steroid with lithium chloride in dimethylformamide. Unexpectedly, the major product was found to have properties typical of a Δ^4-3-ketone. Since dichloro alcohols[1,2] are easily prepared from Δ^5-3β-acetates

(1) (a) F. Cutler, Jr., L. Mandell, D. Shew, J. Fisher, and J. Chemerda, *J. Org. Chem.*, **24**, 1621. 1626, 1629 (1959); (b) Glidden Co., British Patent 778,334, July 3, 1957; *Chem. Abstr.*, **52**, 2106 (1958).

(2) H. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 820 (1956).



and there is frequent need to convert the latter to Δ^4-3-ketones,[3] further examination of this reaction with more familiar products was undertaken.

In the simplest case investigated, treatment of 5α,6β-dichloro-3β-hydroxypregnane-20-one[1a] with lithium chloride in dimethylformamide at 110° for two hours was found to give a mixture of products from which progesterone could be isolated. Similar treatment of 5α,6β-dichloro-16α,17α-oxido-3β-hydroxypregnane-20-one[1b] resulted in introduction of the Δ^4-3-ketone with simultaneous opening of the oxide ring to the 16β-chloro-17α-ol. Regeneration of the oxide in the usual manner with potassium hydroxide gave 47% of 16α,17α-oxido-Δ^4-pregnene-3,20-dione (epoxyprogesterone). Treatment of 5α,6β-dichloro-3β,17α,21-trihydroxypregnane-20-one under these conditions resulted in degradation of the dihydroxyacetone side chain to the 17-ketone. Addition of an excess of lithium carbonate, however, allowed the reaction to proceed selectively to give 17α,21-dihydroxy-Δ^4-pregnene-3,20-dione (cortexolone) in 60% yield.

The facile reaction of the dichlorides involving loss of two molecules of hydrochloric acid is unusual considering the stability of such materials under a variety of conditions.[1a] The lithium ion probably acts as a catalyst in a manner similar to that reported by Holysz[4] for the dehydrohalogenations of α-bromo ketones. The reaction mixture becomes quite acidic due to the hydrogen chloride generation and this is reflected by the formation of a chlorohydrin from the 16,17-epoxide. Apparently, the degradation of the dihydroxyacetone side chain in the attempted formation of cortexolone in the absence of lithium carbonate is also due to this acidity. The carbonate, used by Joly, *et al.*,[5] to temper dehydrohalogenations of α-bromo ketones, was found to buffer satisfactorily the reaction without affecting Δ^4-3-ketone formation. Formation of Δ^4-3-ketones from the dichlorides under these conditions is clearly a non-oxidative process as shown by survival of the unprotected 21-hydroxyl function in the formation of cortexolone.

Calcium carbonate has been used successfully to replace the lithium carbonate but pyridine, surprisingly, prevents formation of Δ^4-3-ketones even though dehydrochlorination takes place as indicated by a negative Beilstein test of the products. The use of lithium carbonate in the absence of lithium chloride has not been investigated. Attempts to form Δ^4-3-ketones from dichloro-3-acetates were unsuccessful; a dibromo alcohol gave a reduced yield.

The yield of Δ^4-3-ketone seems markedly dependent upon the side chain and/or D-ring substitution. Substantial amounts of by-products appearing to be $\Delta^{2,4,6}$-trienes (λ_{max} 294, 306, and 319.5 mμ)[6] are formed in the preparation of progesterone and oxidoprogesterone. In contrast, only small quantities of polyunsaturated materials are formed in the preparation of cortexolone, destruction of the side chain being the major cause for loss of materials.

Modest attempts to influence favorably the ratio of Δ^4-3-ketones to polyunsaturates have been largely unsuccessful. Stannic chloride or anhydrous hydrogen chloride failed to catalyze the elimination. Dimethylacetamide and diethylformamide gave results comparable to dimethylformamide; only a complex mixture of materials other than Δ^4-3-ketones was obtained using formamide. Starting material was recovered largely unchanged from dioxane, possibly because of the low solubility of lithium chloride in this solvent. Only small changes in product composition were noted at reaction temperatures of 75 or 150° provided reactions times were adjusted to the optimum in each case.

Experimental[7]

5α,6β-Dichloro-3β,17α,21-trihydroxypregnane-20-one.—A solution of 3β,17α,21-trihydroxy-Δ^5-pregnene-20-one 3,21-diacetate[8] (14.58 g., 0.0336 mole) in benzene (385 ml.) and pyridine (2.0 ml.) was treated at room temperature with a solution of chlorine (2.64 g., 0.0373 mole) in carbon tetrachloride (32 ml.). Excess chlorine was destroyed by adding cold acetone (5 ml.) saturated with sulfur dioxide. The resulting mixture was poured into cold 5% aqueous hydrochloric acid (400 ml.). The layers were separated and the aqueous layer was extracted with two 50-ml. portions of benzene. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crystalline residue was slurried with methanol and filtered giving 7.09 g. of the crude dichloro acetate, m.p. 190–230° dec. A second crop weighing 3.29 g., m.p. 187–230° dec., was obtained by concentrating the filtrate.

Nitrogen was bubbled through a mixture of the combined crude dichloro acetates (9.03 g., 0.0179 mole) in methanol (696 ml.) at 5–8° for 20 min. A cooled solution of potassium hydroxide (9.03 g., 0.161 mole) in methanol (180 ml.) was purged similarly with nitrogen and added in one portion to the steroid solution. The resulting mixture was stirred for 2 hr. while the temperature was allowed to rise to 25°. A slow stream of nitrogen was bubbled into the solution during this entire time. The resulting mixture was cooled to 10° and adjusted to pH 5.5–6.0 with acetic acid (9.7 ml.). Water (200 ml.) was added and the organic solvent distilled under reduced pressure. The aqueous residue was extracted with four 100-ml. portions of ethyl acetate. The extracts were combined, washed with water, dried, and concentrated

(3) *Cf.*, C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(4) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4435 (1953).

(5) R. Joly, J. Warnant, G. Nomine, and D. Bertin, *Bull. soc. chim. France*, 366 (1958).

(6) J. Romo, H. Ringold, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951).

(7) Melting points were taken in open capillary tubes and are uncorrected.

(8) H. Fuchsand and T. Reichstein, *Helv. Chim. Acta*, **24**, 804 (1941).

under reduced pressure. The residue was treated with boiling methanol (75 ml.). The resulting mixture was cooled in an ice bath and filtered to give 3.75 g. of the dichloro alcohol, m.p. 150–153° dec. A second crop of 2.08 g. was obtained from the filtrate by concentration, m.p. 143–146° dec. The pure sample was obtained by chromatography on a Florisil column eluting with chloroform and diethyl ether. The residue from the combined ether fractions was crystallized from diisopropyl ether and then from pure methanol, m.p. 153–155° dec; λ_{max}^{MeOH} 290 mμ (ε 89); λ_{max}^{KBr} 2.95, 5.85, and 9.67 μ; $[\alpha]^{24}D$ (*c* 1, dioxane) −34°.

Anal. Calcd. for $C_{21}H_{32}Cl_2O_4$: C, 60.14; H, 7.69; Cl, 16.91. Found: C, 60.34; H, 7.97; Cl, 16.73.

17α,21-Dihydroxy-Δ⁴-pregnene-3,20-dione.—Nitrogen was bubbled through a slurry of lithium chloride (1.53 g., 0.036 mole), lithium carbonate (1.82 g., 0.025 mole), and 5α,6β-dichloro-3β,17α,21-trihydroxypregnane-20-one (5.00 g., 0.012 mole) in dimethylformamide (50.0 cc.) for 10 min. to ensure removal of dissolved oxygen. The mixture was then stirred under a nitrogen atmosphere and rapidly heated to 110 ± 2° and held at this temperature 1 hr. The resulting mixture was cooled and evaporated under reduced pressure while water was added simultaneously until nearly all of the dimethylformamide was removed. The resulting mixture was extracted with methylene chloride and the extract washed with water, treated with decolorizing carbon, dried, and concentrated. The residue was crystallized from diethyl ether to give 2.09 g. of crude cortexolone in two crops, m.p. 196–197 and 191–194°, respectively, about 90% pure by paper chromatography (benzene–formamide system). Paper chromatographic analysis indicated that approximately 15% additional product remained in the filtrate. Recrystallization from 2-methyl-4-pentanone gave the pure sample, m.p. 211–213°, identical in all respects to authentic material.

16α,17α-Oxido-Δ⁴-pregnene-3,20-dione.—A mixture of lithium chloride (0.934 g.) and 5α,6β-dichloro-16α,17α-oxido-3β-hydroxypregnane-20-one[1b] (3.05 g., 7.62 moles) in dimethylformamide (30.5 cc.) was heated to and maintained at 110 ± 2° for 2 hr. under a nitrogen atmosphere. The mixture was then cooled to 25°. The resulting solution of products, consisting of about 65% 16β-chloro-17α-hydroxyprogesterone and 35% of a substance appearing to be 16β-chloro-17α-hydroxy-Δ²,⁴,⁶-pregnatriene-20-one based on paper chromatographic mobility (benzene–cyclohexane–propylene glycol system) and ultraviolet absorption, was adjusted to pH 12 with 2 *N* potassium hydroxide. The crude product crystallized spontaneously from the alkaline solution. The crystalline material was filtered, washed with 60% aqueous dimethylformamide, then water, and dried to give 1.89 g., m.p. 183–200°. Recrystallization from methanol gave Δ⁴-3-keto epoxide, m.p. 211° (lit.,[9] m.p. 205–207°), identified by comparison with an authentic sample.

Progesterone.—Treatment of 5α,6β-dichloro-3β-hydroxypregnane-20-one[1a] in a manner similar to the preceding method except omitting the pH adjustment with potassium hydroxide gave a reaction mixture containing progesterone. Extraction with methylene chloride, evaporation of the extract, and slurrying the residue with diisopropyl ether gave a 50% yield of impure crystalline progesterone, m.p. 112–121°. Recrystallization from acetone gave the pure material, m.p. 127–129°, identical to an authentic specimen.

Acknowledgment.—The author expresses his appreciation to Mr. T. Daniels for his technical assistance and to Dr. W. T. Moreland for his many helpful suggestions in the preparation of this manuscript.

(9) P. Julian, E. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).

A Novel Diimide Reduction

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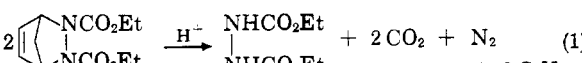
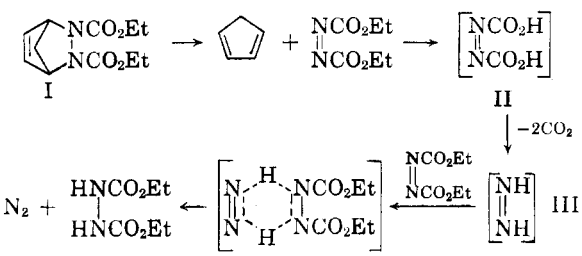
The isolation of diethyl hydrazodicarboxylate from the acid hydrolysis of 2,3-dicarbethoxy-2,3-diazabicyclo[2.2.1]-5-heptene (I) indicated the necessity of further investigation of the mechanism of this reaction. Recent interest in the chemistry and reactivity of diimide[1] led to closer examination of the possible intermediacy of this species in the reaction.

The acid hydrolysis was carried out under conditions of continuous reflux with dilute mineral acid, under nitrogen. The products, either trapped or isolated, were (1) diethyl hydrazodicarboxylate, (2) carbon dioxide, (3) nitrogen, and (4) cyclopentadiene, exactly according to the stoichiometry shown (equation 1), with the exception of cyclopentadiene, which was obtained in less than the theoretical amount as its quinone adduct.[2]



(1)

Two different decomposition routes may be employed to explain this reaction. The first pathway requires an initial reverse Diels-Alder reaction, forming diethyl azodicarboxylate and cyclopentadiene. The diethyl azodicarboxylate then undergoes partial hydrolysis, through the azodicarboxylic acid (II), which readily decarboxylates to produce the active diimide intermediate (III).



The diimide in turn reduces the unhydrolyzed portion of the diethyl azodicarboxylate, thus leading to the formation of diethyl hydrazodicarboxylate.

Any mechanism involving the Diels-Alder adduct in generation of the diimide was shown improbable

(1) (a) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Letters*, **11**, 347 (1961); *J. Am. Chem. Soc.*, **83**, 2957 (1961). (b) S. Hunig, H. R. Muller, and W. Thier, *Tetrahedron Letters*, **11**, 353 (1961). (c) R. Appel and W. Buchner, *Angew. Chem.*, **73**, 807 (1961). (d) E. Schmitz and R. Ohme, *ibid.*, 807. (e) E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3725 (1961). (f) E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *ibid.*, **83**, 4302 (1961). (g) R. S. Dewey and E. E. van Tamelen, *ibid.*, **83**, 3729 (1961).

(2) W. Albrecht, *Ann.*, **348**, 31 (1906).