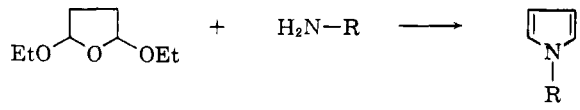
with the appropriate amine in acetic acid. By this means N-triphenylmethylpyrrole and N-(α-naphthylmethyl)pyrrole were synthesized.



It was found that N-(α-naphthylmethyl)pyrrole reacts with acetylenedicarboxylic acid to afford a 9% yield of the Diels–Alder adduct. This is about the same amount of Diels–Alder addition as in the case of N-benzylpyrrole. N-triphenylmethylpyrrole did not react with acetylenedicarboxylic acid.

From the above it is apparent that the hypothesis presented in the early work[1] is incorrect. Further, it would appear that the factor that allows isolation of the Diels–Alder adduct, in these cases, is the insolubility of the zwitter ion formed as a result of Diels–Alder addition. Thus the reaction stops when acetylenedicarboxylic acid is used, whereas with methyl acetylenedicarboxylate the reaction may proceed further as elucidated by the work of Acheson, *et al.*[2,3]

### Experimental[5]

**Triphenylmethylamine.**—A slurry of 30 g. of chlorotriphenylmethane in 600 ml. of liquid ammonia under a Dry Ice condenser was stirred for 6 hr. The ammonia was allowed to evaporate overnight leaving a white crystalline residue. This was triturated with 500 ml. of ether and the ether supernatant washed with 10% sodium carbonate solution and thence water. After drying the ether solution over sodium sulfate, the ether was concentrated *in vacuo*. When about three quarters of the ether had been removed white crystals had formed and were filtered. The filtrate was evaporated to dryness and the residue recrystallized from ether. The total yield was 21.0 g (75.5%) of triphenylamine, m.p. 102–103.5°; reported[6] m.p. 103°.

**N-Triphenylmethylpyrrole.**—Five grams of triphenylmethylamine and 3.0 g. of 2,5-diethoxytetrahydrofuran were added to 40 ml. of cold glacial acetic acid. The mixture was allowed to stand in a refrigerator 2 weeks during which time crystals formed on the sides of the flask. The mixture was filtered and the solid recrystallized twice from benzene giving 2.6 g. (50%) of the pyrrole, m.p. 245–246°. The structure of the material was confirmed by comparison of its infrared and nuclear magnetic resonance spectra with those of N-benzyl- and N-methylpyrrole.

*Anal.* Calcd. for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.94; H, 6.26; N, 4.78.

**Attempted Reaction of N-Triphenylmethylpyrrole with Acetylenedicarboxylic Acid.**—A solution of 1.8 g. of N-triphenylmethylpyrrole and 0.67 g. of acetylenedicarboxylic acid in 20 ml. of dry ether was refluxed for 67 hr. The pyrrole was largely insoluble in the ether (0.1 g. per 20 ml. of ether). Filtration of the hot ether mixture gave 1.7 g. of solid, m.p. 242–245°, which was starting pyrrole.

**α-Naphthylamine.**[7]—In a 1-l. three-necked flask equipped with stirrer and reflux condenser, 28.0 g. of hexamethylenetetramine and 31.0 g. of sodium iodide were added to 320 ml. of hot 95% ethanol. To this solution 35.4 g. of 1-chloromethylnaphthalene was added. The mixture was kept warm (about 50°) and stirred for 3 hr., after which 80 ml. of conc. hydrochloric acid was added and 300 ml. of solvent distilled. The solution was concentrated further *in vacuo* until the residue solidified. This residue was slurried with 500 ml. of water, made alkaline with excess potassium hydroxide (70 g.), and extracted with five 100-ml. portions of ether. The ether was dried over sodium sulfate, concentrated under reduced pressure, and the residue distilled giving 23.5 g. (75%) of the amine, b.p. 95–100° (0.04 mm.); reported,[7] b.p. 200–205° (30 mm.).

**N-(α-Naphthylmethyl)pyrrole.**—In a 100-ml. flask 13.0 g. of α-naphthylmethylamine, 13.2 g. of diethoxytetrahydrofuran, and 20 ml. of glacial acetic acid were refluxed in the dark, under nitrogen, for 1 hr. The dark brown reaction mixture was diluted with 100 ml. of water and extracted with four 100-ml. portions of ether. The ether extract was washed with water, 10% sodium carbonate solution, and dried over sodium sulfate. Evaporation of the ether *in vacuo* gave a dark residue which solidified upon cooling. The residue was recrystallized several times from ethanol giving 7.8 g. (45.5%) of the pyrrole, m.p. 57–58°. It had an infrared spectrum almost identical with that of N-benzylpyrrole.

*Anal.* Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.33; N, 6.76. Found: C, 87.07; H, 6.12; N, 6.82.

**Reaction of N-(α-Naphthylmethyl)pyrrole with Acetylenedicarboxylic Acid.**—A solution of 10.0 g. of N-(α-naphthylmethyl)-pyrrole and 5.5 g. of acetylenedicarboxylic acid in 35 ml. of dry ether was refluxed 24 hr. during which time the solution darkened and a solid precipitated. The hot ether solution was filtered and the yellow residue (2.0 g. 12.9%) treated with charcoal and recrystallized from ethanol and water giving 1.4 g. (9%) of the Diels–Alder adduct, decomposition point, 194°. An infrared spectrum showed, among other absorptions, a band at 2.90 μ and a strong unresolved band between 6.10 and 6.90 μ, indicative of a zwitterion.

*Anal.* Calcd. for: $C_{19}H_{15}O_4N$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.77; H, 4.38; N, 4.32.

(5) Melting points and boiling points are uncorrected. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England. Infrared spectra were determined with a Perkin–Elmer Model 21, double beam, infrared recording spectrophotometer.

(6) C. A. Kraus and R. Rosen, *J. Am. Chem. Soc.*, **47**, 2739 (1925).

(7) This is essentially a combination of the procedures of F. F. Blicke and C. E. Maxwell, *J. Am. Chem. Soc.*, **61**, 1780 (1939) and A. Galat and G. Elion, *ibid.*, **61**, 3585 (1939).

## Facilitated Alkaline Hydrolysis of Diol Monoesters[1]

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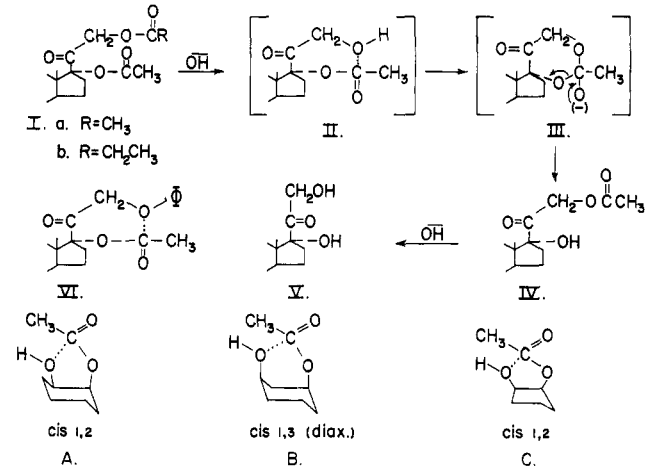
In 1956 H. J. R. noted[2] that 17,21-diacetate esters of steroids possessing the dihydroxyacetone side chain (Ia) undergo complete alkaline hydrolysis with remarkable ease[3] (1.15 equiv. methanolic potassium hy-



(1) This investigation was aided by grants A-4044 and CY 4550, National Institutes of Health.

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

(3) See also (a) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *ibid.*, **74**, 5394 (1952); (b) R. B. Turner, *ibid.*, **75**, 3489 (1953).

droxide, 80 min. 0–5°) while 17α-acetoxy-20-keto-21-desoxy steroids (*e.g.*, 17α-acetoxyprogesterone) require considerably more vigorous[2,4] conditions for saponification. Further, it was also noted[2] that 17-acetate hydrolysis was facilitated by the presence of a 21-phenoxide group (VI) although the ether moiety was untouched by alkali.

Since 21-acyloxy-20-keto steroids are readily saponified it appeared probable that the hydrolysis of the 17,21-diacetate (Ia) proceeded *via* the 17α-acetoxy-21-hydroxy compound (II) followed by intramolecular acetate transfer[5] to C-21 (III, IV) and then finally saponification of the 21-monoester (IV). To determine the mechanism of the diester saponification and to trap reaction intermediates we have investigated the hydrolysis of several substrates under milder conditions.

When 4-pregnene-17α,21-diol-3,11,20-trione 17,21-diacetate (cortisone 17,21-diacetate)[3a] (Ia) was treated for sixteen hours at 25° in aqueous methanol with potassium bicarbonate as base, cortisone 21-monoacetate (IV) and completely saponified cortisone (V) were isolated by Silica-Gel column chromatography in yields of 30 and 5%, respectively. This formation of the 21-monoester further indicated the probability of intramolecular transesterification as an integral part of the diester saponification.

Conclusive evidence for the proposed mechanism was found in the hydrolysis of a mixed ester. 4-Pregnene-17α,21-diol-3,20-dione (substance "S") was converted by propionic anhydride–pyridine to the 21-monopropionate which on treatment with boiling acetic anhydride[3a] gave the 17α-acetate-21-propionate (Ib). The 21-monopropionate moved slightly faster than "S" 21-monoacetate on Silica-Gel thin-layer chromatography in a 30% ethyl acetate–70% benzene system and thus could be readily separated from the latter. Similarly the 17α-acetate-21-propionate moved faster than substance "S" 17,21-diacetate. Hydrolysis of Ib with potassium bicarbonate for sixteen hours, followed by thin-layer chromatographic separation, led to the isolation in a pure state of 27% starting material, 37% completely saponified "S" (V) and 16% of "S" 21-monoacetate (IV), the identity of the latter having been established by direct comparison with an authentic specimen. No 17-acetate-21-ol nor 21-propionate-17-ol could be detected. Compound IV could have been formed only by hydrolysis of the 21-propionate followed by acetate transfer from 17 to 21. The acetate transfer is pictured as a simple addition of the C-21 hydroxyl or probably alkoxide to the ester carbonyl group followed by collapse of the ortho ester (III). In the absence of kinetic data, proton transfer steps have been ignored.

Intramolecular transesterification of this type should be particularly favored in certain cycloalkane derivatives. Molecular models demonstrate that hydroxyl–ester carbonyl interaction is most favorable from a structural viewpoint in cyclohexane derivatives when the hydroxyl groups are in the 1,2-*cis* (A) or 1,3-*cis*-diaxial (B) configurations while in a cyclopentane ring only the *cis*-1,2-diols (C) are favorably disposed for interaction. It is of interest that Kupchan, Slade, and Young[6] found that cholestane-3β,4β-diol 3-monoacetate undergoes ester interchange upon treatment with alkaline alumina.

The facilitated hydrolysis of the 21-phenoxy-17α-acetoxy compound (VI) previously reported[2] is probably due to the inductive effect of phenoxide transmitted through the C-20 ketone.

### Experimental[7]

**4-Pregnene-17α,21-diol-3,20-dione 17-Acetate 21-propionate (Ib).**—A mixture of 4-pregnene-17α,21-diol-3,20-dione (compound "S") (2.2 g.) in propionic anhydride (20 ml.) and pyridine (20 ml.) was heated on the steam bath for 1 hr. The cooled solution was poured into water, stirred for 2 hr., and the resulting precipitate filtered. Crystallization from acetone–hexane gave 2.0 g. of "S" 21-monopropionate, m.p. 247–249°. The infrared spectrum showed bands at 5.73, 5.80, 6.05, 6.2, 8.1, 8.35, and 8.40 μ, the latter two bands serving to differentiate the propionate from "S" 21-monoacetate which had only weak bands at these positions.

*Anal.* Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found C, 71.50; H, 8.63.

The 21-propionate (1.9 g.) was heated for 15 hr. in 50 ml. of boiling acetic anhydride before concentration of the solution *in vacuo*. Ice–water was added and the gummy precipitate filtered and triturated with aqueous methanol, yielding 0.75 g. of Ib, m.p. 210–214°. The analytical specimen from acetone–hexane exhibited m.p. 214–216°. The infrared spectrum exhibited bands at 5.71, 5.78, 5.99, 6.20, 7.9–8.14 (broad triplet), 8.41, and 8.50 μ. The relatively intense bands in the 8.4–8.5-μ region were found in "S" 17,21-diacetate (Ia) as only weak bands. The mixture melting point of Ib with "S" diacetate of m.p. 220–222° was 210–213°.

*Anal.* Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.35; H, 8.12.

**Partial Saponification of Cortisone 17,21-Diacetate.**—A suspension of 0.5 g. of cortisone 17,21-diacetate[3a] in 80 ml. of methanol was treated with a solution of 0.5 g. of potassium bicarbonate in 10 ml. of water, the mixture flushed with nitrogen, stoppered, and shaken for 16 hr. at room temperature. The clear solution was neutralized with 0.3 ml. of glacial acetic acid and concentrated *in vacuo* to a small volume. The addition of water gave 391 mg. of material which was chromatographed on 20 g. of silica gel. Elution with 10–25% ethyl acetate in benzene gave 153 mg. of cortisone 21-monoacetate, m.p. 231–240°, while 50% ethyl acetate–benzene gave 27 mg. of cortisone alcohol, m.p. 219–223°. Identity was established in both cases by comparison with authentic samples.

**Partial Saponification of 4-Pregnene-17α,21-diol-3,20-dione 17-Acetate 21-Propionate (Ib).**—A mixture of Ib (50 mg.) in 8 ml. of methanol and potassium bicarbonate (50 mg.) in 1 ml. of water was stirred for 16 hr. under nitrogen. Acetic acid (0.1 ml.) and water (50 ml.) were added and the product isolated by ethyl acetate extraction. The residue, in chloroform solution, was applied in a line to a 25 cm. wide, 1 mm. thick, silica plate which was developed (ascending) with 30% ethyl acetate–70% benzene. The three major zones which were detected with the ultraviolet lamp were scraped and eluted individually. In the order of decreasing mobility the zones gave recovered Ib, (13.4 mg., 27%, m.p. 214–216°), slightly impure "S" 21-monoacetate (9.7 mg.) and free "S" alcohol (V) (14.5 mg., 37%, m.p. 209–212°). Rechromatography of the central zone gave 7.1 mg., 16%, of pure "S" 21-monoacetate (IV), m.p. 240–242°, whose infrared spectrum and chromatographic behavior were identical with an authentic specimen while the compound was slightly more polar than the 21-monopropionate.

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(4) H. J. Ringold, B. Loken, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 817 (1956).

(5) This same mechanism has been suggested by L. Fieser and M. Fieser, "Steroids," Reinhold Corp., New York, N. Y., 1959, p. 680.

(6) S. M. Kupchan, P. Slade, and R. J. Young, *Tetrahedron Letters*, **24**, 22 (1960).

(7) The melting points are uncorrected and the infrared spectra were obtained in potassium bromide pellet.