[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Application of the Passerini Reaction to Steroid Ketones[1]

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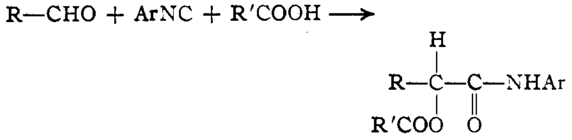
The reaction of aldehydes and ketones with aryl isocyanides in the presence of carboxylic acids was shown by Passerini[2] to yield α-acyloxy derivatives of N-arylamides according to the equation:

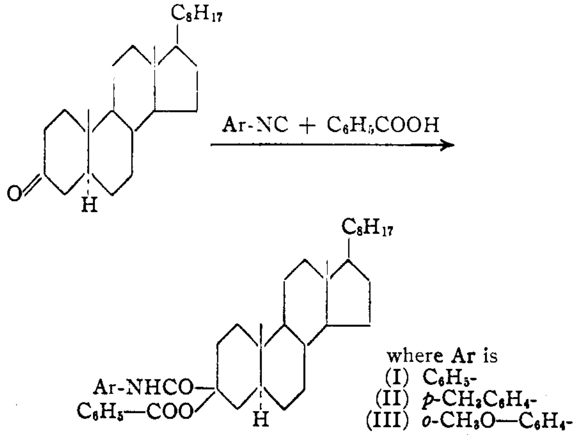


$$\mathrm{R{-}CHO + ArNC + R'COOH \longrightarrow R{-}\overset{\displaystyle H}{\underset{\displaystyle R'COO}{C}}{-}\underset{\displaystyle O}{\underset{\Vert}{C}}{-}NHAr}$$

Since the reaction was shown to apply well to cyclic ketones it appeared that it might serve as a convenient first step toward the building up of oxygenated side chains on the sterol nucleus. One of the most desired applications would be to the keto group of dehydroandrosterone, 3-(β)-hydroxy-5-androsten-17-one; however, in our hands neither *p*-tolyl nor *o*-anisyl isocyanide will react with this molecule or its 3-benzoyloxy derivative in the presence of benzoic acid. This failure must be ascribed to the blocking effect of substituents at position 13 in the sterol nucleus, and indeed it has previously been observed[2] that camphor, a similarly substituted cyclopentanone, fails to react.

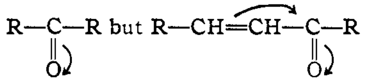
Another serious limitation to the reaction was discovered in attempting to apply it to cholestenone, 4-cholesten-3-one. This α,β-unsaturated ketone could not be made to react with either *p*-tolyl or *o*-anisyl isocyanides in the presence of benzoic acid. Two other α,β-unsaturated carbonyl compounds, benzalacetophenone and crotonaldehyde, also failed to react with these reagents. These unsaturated compounds may be determined by means of the polarograph[3] and aliquots of the reaction mixtures were polarographed at various intervals up to 168 hours. No reduction in the heights of the waves due to the carbonyl compounds was observed except in the case of the crotonaldehyde and this was determined to be due to polymerization.

It has been possible to prove that the failure of cholestenone to react is due not to steric hindrance but to the α,β-unsaturation, by successfully applying the reaction of three different isocyanides to the saturated ketone, 3-cholestanone, in the presence of benzoic acid according to the equation given.



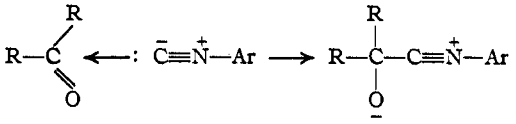
where Ar is
(I) C_6H_5-
(II) *p*-$CH_3C_6H_4$-
(III) *o*-CH_3O—C_6H_4-

Insufficient evidence is now at hand to describe the role of the double bond in preventing the reaction, but it seems reasonable to assume that it is associated with a neutralization of the electrophilic center at the carbonyl group



$$\mathrm{R{-}\underset{O}{\underset{\Vert}{C}}{-}R}\ \text{but}\ \mathrm{R{-}CH{=}CH{-}\underset{O}{\underset{\Vert}{C}}{-}R}$$

o-Anisyl isocyanide was tried with the unsaturated compounds in the hope that it might provide a sufficiently strong nucleophilic center to affect reaction at either the carbonyl group or the beta carbon atom. This effort was prompted by the possibility that the primary step in the reaction may be similar to that of the cyanohydrin reaction[4] with the permanent dipole of the isocyanide taking the role of the cyanide ion.



$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle O}{C}} \longleftarrow :\overset{-}{C}{\equiv}\overset{+}{N}{-}Ar \longrightarrow R{-}\overset{\displaystyle R}{\underset{\displaystyle \overset{|}{O}^{-}}{C}}{-}C{\equiv}\overset{+}{N}{-}Ar}$$

Although this line of attack has been disappointing, it is hoped that research in progress will throw further light on the mechanism of the reaction.

The derivatives of 3-cholestanone have proved to be remarkably stable with respect to hydrolysis of the amide group. The ester group is hydrolyzed with ease, but all attempts to cleave the resulting α-hydroxyanilide have met with failure. Acids are without effect as are alkaline conditions sufficiently severe to dissolve considerable silica from the Pyrex reaction flasks. Similar difficulties are encountered with simple α-hydroxy amides bearing two alkyl substituents on the α-carbon atom.[5]

The hydroxy-anilide, V, is also rather stable to heat, and indeed may best be purified by sublima-

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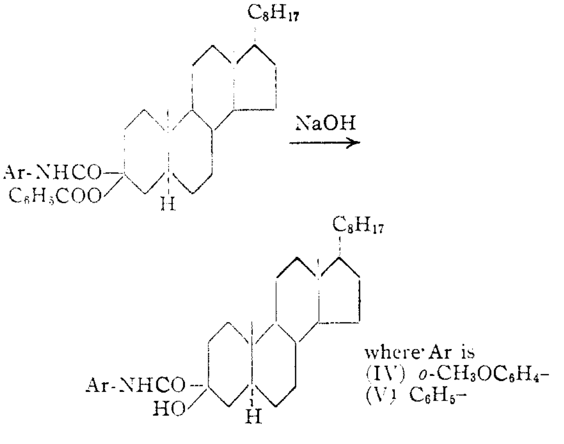
(1) This investigation was supported by a grant from the Abbott Fund of Northwestern University.

(2) Mario Passerini, *Gazz. chim. ital.*, **51**, 181 (1921); **53**, 410 (1923); **54**, 529 (1924).

(3) Adkins and Cox, THIS JOURNAL, **60**, 1151 (1938).

(4) Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); Jones, *ibid.*, **105**, 1560 (1914).

(5) Stoughton, THIS JOURNAL, **63**, 2376 (1941).



tion in vacuum by heating at 220–255° for four hours.

Experimental Part

Preparation of Compounds.—The isocyanides were obtained by reaction of the appropriate amines with chloroform and powdered alkali according to published procedures. After purification they were sealed and stored at −15° until used. The boiling points of the isocyanides were as follows: phenyl,[6] 64° at 20 mm.; *p*-tolyl,[7] 89–92° at 25 mm.; *o*-anisyl,[8] 107–110° at 15 mm. Cholestenone, m. p. 80–81°, was obtained from a commercial product[9] after two crystallizations from methanol-acetone followed by vacuum sublimation.

3-Cholestanone, m. p. 128–129°, was prepared by catalytic reduction of cholesteryl acetate followed by saponification and oxidation.[10] In our hands the reduction of cholesteryl acetate is superior to that of the unacetylated sterol.

Dehydroandrosterone, m. p. 146–147°, was obtained by hydrolysis of its semicarbazide.[11] Benzoyl chloride converted the keto-alcohol into the 3-benzoyloxy compound,[12] m. p. 257°.

Reaction of Isocyanides with Cholestanone.—A mixture of 0.5 g. (1.30 × 10⁻³ mole) of cholestanone, 0.2 g. (1.64 × 10⁻³ mole) of benzoic acid, and 0.46 g. (3.94 × 10⁻³ mole) of *p*-tolyl isocyanide was dissolved in the minimum quantity of ether and allowed to stand at room temperature for five days. Steam was then passed through the mixture to remove the ether and excess isocyanide. The product, 3-benzoyloxy-3-carb-*p*-toluididocholestane, II, was crystallized from alcohol in long white needles. The yield was 0.342 g. (43.0%), m. p. 203–207°. A sample was recrystallized to constant melting point, 206–207.5°, for analysis.

Anal.[13] Calcd. for $C_{12}H_{59}O_3N$: C, 80.61; H, 9.50; N, 2.24. Found: C, 80.36; H, 9.61; N, 2.96.

o-Anisyl isocyanide, 7.8 millimoles, was treated with equivalent quantities of benzoic acid and cholestanone in ether solution. After six days at room temperature the product was worked up as described above. The yield of crude material, m. p. 118°, was 53%. This was recrystallized to constant melting point, 129–130°, and the yield of pure product, 3-benzoyloxy-3-carb-*o*-anisididocholestane, III, was 26%. A mixed melting point with cholestanone, m. p. 128–129°, was 121°.

Anal.[13] Calcd. for $C_{42}H_{59}O_4N$: C, 78.58; H, 9.27; N, 2.18. Found: C, 80.49; H, 9.86; N, 1.85.

Phenyl isocyanide reacted in a similar manner with cholestanone and benzoic acid. After seven days the yield of recrystallized 3-benzoyloxy-3-carbanilidocholestane, I, m. p. 179–180°, was 30%. The specific rotation was +42° (20 mg. made up to 2.0 ml. with dibutyl ether, $\alpha^{25}D$ + 0.42°; *l*, 1 dm.).

Anal.[13] Calcd. for $C_{41}H_{67}O_3N$: C, 80.41; H, 9.39; N, 2.29. Found: C, 81.00; H, 9.63; N, 2.80, 2.32.[14]

Semimicro Zerewitinoff Analysis.—Calculated for one active hydrogen: 12.7 mg. requires 2.07 × 10⁻⁵ mole of methane. Found: 1.86 × 10⁻⁵ mole of methane.

Hydrolysis of the Cholestane Derivatives.—3-Hydroxy-3-carb-*o*-anisididocholestane, IV, was obtained by refluxing 500 mg. of the benzoate ester for one hour with 10 ml. of 0.5 *N* alcoholic potassium hydroxide. The product was recovered by dilution with water and filtering. The yield of crude product was 350 mg. (83.6%). A sample was recrystallized from alcohol for analysis, m. p. 211–212°.

Anal.[13] Calcd. for $C_{36}H_{55}O_3N$: C, 78.15; H, 10.32; N, 2.16. Found: C, 77.35; H, 9.77; N, 2.93.

A 200-mg. sample of this primary hydrolysis product was changed by neither a 100-hour period of refluxing with 0.5 *N* alcoholic potassium hydroxide, nor a 72-hour period of refluxing with 7 *N* sulfuric acid in 75% alcohol.

3-Hydroxy-3-carbanilidocholestane, V, was obtained by refluxing 2.0 g. of its benzoate ester with 1 *N* butanolic potassium hydroxide for five hours. The mixture was neutralized with hydrochloric acid and steam distilled to remove the butyl alcohol. The solid residue was collected on a filter, and the organic material extracted away from silica with hot chloroform. After evaporation of the chloroform the residue was crystallized from 25 ml. of benzene. The yield of white plates, m. p. 232°, was 400 mg. The product was further purified by sublimation at 1 mm. in a short-path apparatus using a bath temperature of 225–255° for two hours. From 64 mg. of crude product 41 mg. of sublimate, m. p. 232.5–233°, was obtained. The compound is insoluble in ether, alcohol, petroleum ether and ethyl acetate. It is moderately soluble in dioxane and in warm benzene or chloroform.

Anal.[14] Calcd. for $C_{34}H_{53}O_2N$: C, 80.53; H, 10.47; N, 2.76. Found: C, 80.26; H, 10.61; N, 2.79.

Semimicro Zerewitinoff Analysis.—Calculated for two active hydrogens: 28.5 mg. requires 11.22 × 10⁻⁵ mole of methane. Found: 10.9 × 10⁻⁵ mole of methane. The specific rotation was +35° (29.4 mg. made up to 2.09 ml. with dioxane, $\alpha^{25}D$ + 0.38°; *l*, 1 dm.).

Acknowledgment.—We are indebted to Mr. Charles J. Albisetti for translation of the Italian literature, and to Patty Campbell Weiss for some of the preliminary experimental work.

Summary

1. 3-Cholestanone has been shown to react with aryl isocyanides in the presence of benzoic acid to produce substituted 3-benzoyloxy-3-carbanilidocholestanes.

2. Dehydroandrosterone, dehydroandrosterone benzoate and cholestenone fail to react with isocyanides in the presence of benzoic acid.

3. Alkaline hydrolysis of 3-benzoyloxy-3-carbanilidocholestane is effective only at the ester linkage.

EVANSTON, ILLINOIS RECEIVED MAY 21, 1945

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[6] Nef, *Ann.*, **270**, 267 (1892).

[7] Hammick, New, Sidgewick and Sutton, *J. Chem. Soc.*, 1876 (1930).

[8] Lindemann and Wiegrebe, *Ber.*, **63**, 1650 (1930).

[9] This was kindly furnished by Dr. E. L. Foreman of Lakeside Laboratories.

[10] "Organic Syntheses," 2nd ed., Coll. Vol. II, pp. 139, 191.

[11] This was kindly furnished by Dr. P. L. Julian of The Glidden Co.

[12] Wallis and Fernholz, THIS JOURNAL, **57**, 1504 (1935).

[13] Microanalysis by Dr. T. S. Ma.

[14] Microanalysis by Mrs. Margaret Ledyard and Miss Winifred Brandt.