

1.60) with stirring at room temperature according to the directions for the preparation of 6-ketocholestanyl acetate.³ The reaction flask was then cooled in an ice-salt-bath and the remaining nitric acid mixture added with vigorous stirring during one hour. Stirring was continued for an additional half-hour and then the solution was poured into ice and water. The yellow precipitate was filtered, washed well with water and air-dried, m.p. 120–125° (dec.).

The crude nitrate was directly reduced in acetic acid solution (100 cc.) by adding 12.5 g. of zinc dust and heating on the steam-bath for two hours and then under reflux for 10 hours. After dilution with water the product was isolated by ether extraction and the resulting brown oil obtained after removal of the solvent was directly hydrolyzed with alcoholic hydrochloric acid for 1.5 hours. On working up the reaction only 520 mg. of crude oil was obtained, which was purified by chromatography on alumina in 25% benzene-hexane solution. The fraction eluted with 100% ben-

zene gave 190 mg. of material, m.p. 174–175° after recrystallization from aqueous methanol. A mixture of this material with that isolated from the oxidation of androstanediol diacetate (m.p. 177–178°) melted at 173–176°.

Isolation of 3 β ,5,17 β -Androstanetriol 3,17-Diacetate.—Fraction 3 of the previously mentioned chromatogram of the oxidation products of androstanediol diacetate was recrystallized from hexane and 1.6 g. (5.3%) of material, m.p. 180–182°, $[\alpha]_{D}^{25} -9^{\circ}$.

Anal. Calcd. for C₂₃H₃₈O₅: C, 70.4; H, 9.3. Found: C, 70.2; H, 9.5.

Since the physical properties of this compound were the same as those of the androstane-3 β ,5 α ,17 β -triol 3,17-diacetate previously described, a mixture of the two substances was made and this showed no depression of the melting point.

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NOTES

Reduction of Acyl Cyanides with Lithium Aluminum Hydride

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Acyl cyanides have been hydrogenated to primary amino alcohols in good yields² but this method has not enjoyed wide use because of its relatively complicated mode of execution. It has now been observed that the same result can be achieved by reduction with lithium aluminum hydride. By this procedure it is also possible to preserve in the amino alcohols such substituents as aromatic halogen atoms which could be hydrogenolyzed in catalytic methods.

The preparation of amino alcohols from acyl cyanides complements related reduction methods of cyanohydrins which lead to amino alcohols^{3–6} or amines.^{4,7}

Experimental⁸

2-Phenylethanolamine.—A solution of 7.35 g. (0.056 mole) of benzoyl cyanide⁹ in 100 ml. of dry ether was added dropwise to a stirred solution of 10 g. (ca. 0.26 mole) of lithium aluminum hydride in 300 cc. of ether so that refluxing was maintained. After another four hours of boiling the mixture was decomposed with water, and a 30% sodium hydroxide solution was added in small portions until a granular precipitate appeared. The latter was filtered, washed with ether, and the oily residue from the combined ether layers was distilled under reduced pressure. It yielded 6.5 g. (86%) of a colorless solid which, after recrystallization from benzene-petroleum ether melted at 56.5–58°.¹⁰

Anal. Calcd. for C₉H₁₁NO: C, 70.04; H, 8.08. Found: C, 69.81; H, 8.32.

- (1) Parke, Davis & Co. Predoctoral Fellow.
- (2) K. Kindler and W. Peschke, *Arch. Pharm.*, **269**, 581 (1931).
- (3) F. Wolfheim, *Ber.*, **47**, 1440 (1914).
- (4) J. S. Buck, *THIS JOURNAL*, **56**, 2593 (1933).
- (5) H. R. Nace and B. B. Smith, *ibid.*, **74**, 1861 (1952).
- (6) H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).
- (7) W. H. Hartung, *THIS JOURNAL*, **50**, 3370 (1928).
- (8) All melting points are corrected.
- (9) T. S. Oakwood and C. A. Weisberger, *Org. Syntheses*, **24**, 14 (1944).
- (10) Literature (cf. 2), m.p. 57°; N-benzamide derivative 149°.

When in another run only 30% excess of lithium aluminum hydride was used, the yield was reduced to 30%.

The N-benzoyl derivative crystallized from ethanol, m.p. 148–149°.¹⁰

p-Chlorobenzoyl Cyanide.—A mixture of 65.5 g. (0.374 mole) of p-chlorobenzoyl chloride and 40.5 g. (0.45 mole) of cuprous cyanide was heated at 210–220° for one hour and then distilled under reduced pressure. The yield of colorless solid was 24.9 g. (40%), m.p. 37–40°. Redistillation raised the melting point to 41–42.5°.¹¹

Anal. Calcd. for C₇H₄ClNO: C, 58.03; H, 2.44. Found: C, 57.76; H, 2.35.

2-(p-Chlorophenyl)-ethanolamine.—Reducing 8.3 g. (0.05 mole) of p-chlorobenzoyl cyanide with 10 g. (ca. 0.26 mole) of lithium aluminum hydride in a total of 300 ml. of dry ether for three hours, and working the reaction mixture up as described above, 7.7 g. (89%) of a colorless solid was obtained which crystallized from benzene, m.p. 93.5–94.5°.

Anal. Calcd. for C₈H₁₀ClNO: C, 55.98; H, 5.87. Found: C, 55.82; H, 5.84.

The benzoyl derivative crystallized from ethanol, m.p. 215.5–217.5°.

Anal. Calcd. for C₁₅H₁₄ClNO₂: C, 65.34; H, 5.12. Found: C, 65.15; H, 5.34.

(11) M. R. Zimmermann, *J. prakt. Chem.*, [2] **66**, 353, 383 (1902); reports m.p. 40°.

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Tetraethyl Pyrophosphite as a Reagent for the Preparation of Anilides

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Tetraethyl pyrophosphite has been shown to be a useful reagent for forming peptide bonds.¹ We have found that it can be conveniently used to prepare anilides in good yield (Table I).

Experimental

Tetraethyl pyrophosphite was prepared as previously described.¹

(1) G. W. Anderson, J. Blodinger and A. D. Welcher, *THIS JOURNAL*, **74**, 5304 (1952).

TABLE I
 CARBOXYLIC ANILIDES PREPARED USING TETRAETHYL PYROPHOSPHITE

Anilides	Method of purification	Yield, %	M.p., °C.
Benzanilide	Crystallized from toluene	97	160-161 ^e
Acetanilide	Washed with saturated sodium bicarbonate	97	110-111 ^c
Carbobenzoxy-DL-phenylalanine anilide	Crystallized from toluene	98	158-160 ^d
<i>o</i> -Chloroacetanilide	Washed with sodium bicarbonate and recrystallized from ether	75	86-87 ^e
<i>N</i> -Methylacetanilide	Crystallized from reaction mixture and recrystallized from alcohol	64	98-99 ^f
Salicylanilide ^b	Washed with 1/2 saturated sodium bicarbonate—recrystallized from 50% alcohol	69	134-135 ^g
2-Phenylcinchoninanilide	Washed with saturated sodium bicarbonate and reprecipitated from alcohol with water	77	201-202 ^h

^a O. Wallach and M. Hoffmann, *Ann.*, **184**, 80 (1876). ^b No solvent was used in this reaction. ^c Authentic sample U.S.P. grade had m.p. 110-111°. ^d G. W. Anderson, J. Blodinger, R. W. Young and A. D. Welcher, *THIS JOURNAL*, **74**, 5307 (1952). ^e Doht, *Monatsh.*, **27**, 221 (1906); "Beilstein," Vol. XII, p. 299, gives m.p. 88°. ^f W. Stadel, *Ber.*, **19**, 1947 (1886). ^g R. Wanstrat, *ibid.*, **6**, 336 (1873), gives m.p. 134-135°. ^h A. Rojahn and J. Schotten, *Arch. Pharm.*, **264**, 337-347 (1926); *Chem. Zentr.*, **97**, II, 1, 415 (1926), give m.p. 198°.

The preparation of benzanilide was investigated to find optimum conditions. The effect of the order of reagent addition, the period of heating, the relative proportions of reagents and the presence or absence of a solvent upon the ease of isolation and yield of product was determined. The use of a 10% excess of tetraethyl pyrophosphite was favorable, but when increased to 50% the yield was lowered and the product was more difficult to purify. Increasing the period of heating with a 10% excess of tetraethyl pyrophosphite in toluene was favorable, but with a 50% excess the yield was decreased. The order of addition did not affect the yield. The following procedure gave a product that was readily purified and in the higher yield. A solution of 1.22 g. (0.01 mole) of benzoic acid, 0.93 g. (0.01 mole) of aniline and 2.83 g. (0.011 mole) of tetraethyl pyrophosphite in 15 cc. of dry toluene was refluxed for 2 hours. The mixture was cooled in an ice-bath and a solid precipitated. After drying this weighed 1.47 g., m.p. 160-161°. The distillation of the toluene yielded an oil which crystallized after being washed with 10 cc. of saturated sodium bicarbonate solution; wt. 0.45 g., m.p. 160-161°. The total yield was 97%. A control reaction, run under the same conditions in the absence of tetraethyl pyrophosphite, gave no product and a 97% recovery of benzoic acid. The anilides listed in Table I were made using essentially this same procedure.

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The Preparation of Isonicotinic and Picolinic Acids

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Although several references appear in the literature concerning the oxidation of 2-picoline to picolinic acid by use of selenium dioxide,^{2,3} no experimental references are recorded for a similar preparation of isonicotinic acid from 4-picoline. A recent article⁴ makes note of the isolation of this acid when selenium dioxide was used to prepare isonicotinaldehyde from 4-picoline but no details of this reaction are given.

Since another problem in this Laboratory involved the use of selenium dioxide as an oxidizing agent for methyl-substituted nitrogen hetero-

cyclics, it was of interest to apply this reaction to the preparation of isonicotinic acid from 4-picoline. It has been found that oxidations of this type can be carried out successfully using diphenyl ether as the solvent. The following method makes possible a convenient preparation of isonicotinic acid from 4-picoline in 57% yield with no aldehyde contamination. The preparation of picolinic acid gives yields of only 25-30% while similar attempted oxidations of 3-picoline were unsuccessful.

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Experimental⁵

Isonicotinic Acid.—Twenty grams (0.216 mole) of 4-picoline was dissolved in 100 ml. of diphenyl ether and placed in a three-neck flask equipped with a stirrer, condenser and glass plug. The solution was heated to 155°. To the stirred mixture 39.6 g. (0.351 mole, 10% excess) of selenium dioxide was added portionwise over a period of 15 minutes. The reaction temperature was then raised to 185° and the reaction continued at this temperature for 30 minutes. At the end of this time the diphenyl ether was decanted from the precipitated selenium-isonicotinic acid residue and the residue brought onto a suction filter and washed with 75 ml. of low boiling ligroin.

The black selenium acid residue was ground to a powder and extracted with three 100-ml. portions of boiling water. The fractions were combined and upon cooling in ice tan crystals of isonicotinic acid formed. The yield was 15.1 g. (57%). No isonicotinic acid was recovered from the diphenyl ether. A melting point of this substance was approximately 310°. Several literature references give the m.p. of this compound from 308 to 317°.

Picolinic Acid.—In a manner analogous to the above preparation 10 g. (0.108 mole) of 2-picoline was dissolved in 50 ml. of diphenyl ether and treated with 17.8 g. (0.16 mole) of selenium dioxide at a temperature of 130° for three hours. At the end of this time the hot diphenyl ether solution was filtered and diluted with 60 ml. of high boiling ligroin. On cooling 3.5 g. (26%) of cream colored crystals, m.p. 132-135°, were obtained. One gram of this substance was recrystallized from a mixture of 40 ml. of benzene and 5 ml. of ligroin (60-75°). The m.p. was 134-135°. Picolinic acid is reported as melting at 134.5-136°.

The precipitated selenium residue was extracted twice with 75 ml. of benzene-ligroin mixture (60 ml.-15 ml.). From the combined extracts was obtained a yellow solid weighing 1.3 g. Recrystallization of this solid from 60 ml. of benzene-alcohol (50 ml.-10 ml.) gave a white solid which melted at 117-119° and which apparently contained selenium

(1) Abstracted from a thesis by R. S. Yunghans presented to the Graduate Council of DePauw University in partial fulfillment of the requirements for the M.A. degree, June, 1952.

(2) M. Henze, *Ber.*, **67**, 750 (1934).

(3) W. Borsche and H. Hartman, *ibid.*, **73**, 839 (1940).

(4) H. H. Fox, *J. Org. Chem.*, **17**, 555 (1952).

(5) The melting points are uncorrected.