Alkylations of α-Dimethylaminophenylacetonitriles and Hydrolysis to Desoxybenzoins[1]

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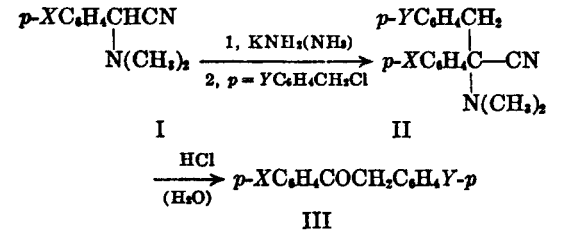
α-Dimethylaminophenylacetonitrile (I. X = H) has recently[2] been benzylated to form II ($X = Y =$ H), which was hydrolyzed to give desoxybenzoin (Equation 1).



These two types of reaction have now been extended as summarized in Table I. This table shows that the yields of the alkylation products II from I and the desoxybenzoins from II were excellent.

TABLE I

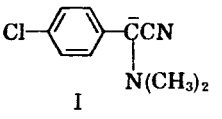
YIELDS OF II AND III IN EQUATION 1

X	Y	II	III
H	H	91[a]	90[a]
Cl	H	96	92
OCH_3	H	80[b]	90
H	Cl	(100)[b]	90

[a] See Ref. 2. [b] Crude alkylation product.

The benzylation of the *p*-chloroaminonitrile I (X = Cl) was of particular interest, since the benzyne type of reaction involving dehydrochlorination[3] was possible. Not only did the amide ion ionize preferentially the α-hydrogen of the aminonitrile, but the resulting intermediate carbanion I′ containing *p*-chlorine did not undergo the benzyne reaction even though excess amide ion was present during the addition of the aminonitrile. Apparently the negative charge on I′ deactivated the ring hydrogens that would be involved in the latter reaction.[4]

Neither was the alkylation of the unsubstituted aminonitrile I (X = H) with *p*-chlorobenzyl chloride accompanied by the benzyne reaction, but excess amide was presumably not present in this reaction. The alkylation product II (X = H, Y = Cl) apparently underwent dehydrocyanation readily, and it was not isolated sufficiently pure for analysis. This was not surprising as even the unsubstituted benzylation product II ($X = Y$ = H) has been dehydrocyanated to form the corresponding enamine.[2]



I

The over-all reaction (equation 1) may be useful for the synthesis of certain substituted desoxybenzoins, which have generally been prepared by the action of benzyl Grignard reagents on appropriate benzamides[5] or from the Friedel-Crafts reaction of phenylacetyl chlorides with aromatic compounds.[6]

EXPERIMENTAL[7]

Alkylations and hydrolyses. (*A*) X = Cl, Y = H. To a stirred solution of 0.05 mole of potassium amide[8] in 250 ml. of commercial anhydrous liquid ammonia was added a solution of 9.75 g. (0.05 mole) of aminonitrile I (X = Cl)[9] in 100 ml. of anhydrous ether followed, after 5 min., by 6.3 g. (0.05 mole) of benzyl chloride in 50 ml. of ether. After 5 min., the ammonia was removed (steam bath) as an equal volume of ether was added. The resulting ether suspension was filtered, and the ether was removed. The residue was recrystallized from hexane to give, in two crops, 13.6 g. (96%) of 2 - (*N,N* - dimethylamino) - 2 - (4 - chlorophenyl) - 3-phenylpropionitrile (II. X = Cl, Y = H), m.p. 104–107.5° and at 105–107° after several recrystallizations from hexane.

Anal. Calcd. for $C_{17}H_{17}N_2Cl$: C, 71.69; H, 6.02; N, 9.84; Cl, 12.54. Found: C, 71.52; H, 6.00; N, 9.71; Cl, 12.53.

Hydrolysis of 1.0 g. of this compound was effected by heating a solution of it in 25 ml. of ethanol and 50 ml. of 6*N* hydrochloric acid on the steam bath for 20 hr. The cooled solution was diluted with water to give a white solid which, after four crystallizations from ethanol, afforded 0.74 g. (92%) of 4-chloro-α-phenylacetophenone (III. X = Cl, Y = H), m.p. 106–106.5° (lit. m.p. 106–107°,[6a] and 107.5°).[6b]

(*B*) $X = OCH_3$, Y = H. Aminonitrile I ($X = OCH_3$)[9] was benzylated essentially by the procedure described in (A). The ether suspension obtained on replacing the ammonia with ether was shaken with 50 ml. of water, and the two layers were separated. The ether layer was dried over anhydrous magnesium sulfate, and the solvent removed. The residue was taken up in 50 ml. of hexane, and the solution cooled in a Dry Ice–acetone bath to give a glassy precipitate, which crystallized on warming slowly to 0°. The precipitate was collected and dried to give 11.2 g. (80%) of 2-(*N,N*-dimethylamino)-2-(4-methoxyphenyl)-3-phenylpropionitrile (II. $X = OCH_3$, Y = H), m.p. 49–54° and 51.5–53° after two further recrystallizations from hexane.

(1) Supported by National Institutes of Health Grant CY-4455(C-2).

(2) C. R. Hauser, H. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, 82, 1786 (1960).

(3) See J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughn, *J. Am. Chem. Soc.*, 75, 3290 (1953).

(4) See J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, 83, 1694 (1961).

(5)(a) E. Ney, *Ber.*, 21, 2450 (1888). (b) P. Petrenko-Kritschenko, *Ber.*, 25, 2240 (1892).

(6)(a) D. Y. Curtin and P. I. Pollak, *J. Am. Chem. Soc.*, 73, 992 (1951). (b) S. S. Jenkins and E. M. Richardson, *J. Am. Chem. Soc.*, 55, 1618 (1933).

(7) Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(8) See C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, 80, 6360 (1958).

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Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.12; H, 7.19; N, 10.00. Found: C, 77.16; H, 7.28; N, 10.05.

Hydrolysis of 7 g. of this compound was effected by heating it in 50 ml. of 6*N* hydrochloric acid on the steam bath for 8 hr. The cooled mixture was filtered, and the solid was recrystallized from methanol-water to give 5.1 g. (90%) of 4-methoxy-α-phenylacetophenone (III. $X = OCH_3$, $Y = H$), m.p. 75–76.5° (lit. m.p. 76°,[5a] and 77–78°).[10]

(*C*) $X = H$, $Y = Cl$. Aminonitrile I ($X = H$)[2] was alkylated on the 0.2-mole scale with *p*-chlorobenzyl chloride essentially by the procedure described in (*A*). The liquid ammonia was evaporated from the reaction product and the residue taken up in ether. After filtering to remove inorganic salts, the ether solution was dried over magnesium sulfate. The solvent was removed to leave 57 g. (100%) of the crude alkylation product as a light yellow oil. A sample of this oil was dissolved in hexane and the solution cooled in a Dry Ice–acetone bath to precipitate a solid, but the pure product was not isolated. The combined oil was dissolved in 105 ml. of concd. hydrochloric acid and the solution refluxed overnight. The mixture was cooled and filtered to give 41.3 g. (90%) of α-(4-chlorophenyl)acetophenone (III. $X = H$, $Y = Cl$), m.p. 133–136° and at 135.5–136° after recrystallization from ethanol (lit. m.p. 133°).[5b,11]

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Some α-Dialkylaminophenylacetonitriles and Corresponding Amino Acids and Aminoamides[1]

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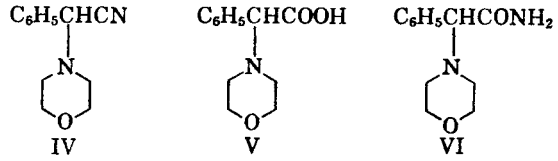
Recently[2] α-dimethylaminophenylacetonitrile (Ia) was prepared from benzaldehyde, dimethylamine, and sodium cyanide through the sodium bisulfite addition compound of the aldehyde, and hydrolyzed to amino acid IIa.

p-XC_6H_4CHCN	p-$XC_6H_4CHCOOH$	p-$XC_6H_4CHCONH_2$
$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$
Ia. $X = H$	IIa. $X = H$	IIIa. $X = H$
Ib. $X = Cl$	IIb. $X = Cl$	IIIb. $X = Cl$
Ic. $X = OCH_3$		IIIc. $X = OCH_3$

We have synthesized aminonitriles Ib and Ic, hydrolyzed Ib to amino acid IIb, and converted all three of the aminonitriles Ia–c to the corresponding aminoamides IIIa–c. Also aminonitrile IV was prepared from the appropriate reagents and converted to amino acid V and aminoamide VI. The yields were good to excellent.



IV V VI

In the synthesis of the aminonitriles 25% aqueous dimethylamine was used instead of the anhydrous amine employed earlier.[2] The initial formation of the aldehyde-bisulfite compound seems advantageous especially for solid aldehydes. Even with benzaldehyde the yield of Ia was higher (94%) than that (75%) obtained without the use of the bisulfite.[3]

Whereas ordinary nitriles can be hydrolyzed to the corresponding acids with dilute sulfuric acid, aminonitrile Ia undergoes some reversion to benzaldehyde (27%) even with 50% refluxing sulfuric acid. The conversion of Ia, Ib, and IV to the corresponding amino acids was accomplished by treatment with more concentrated sulfuric acid. However, aminonitrile Ic produced only water-soluble tars; apparently sulfonation and/or cleavage of the ether group occurred. This method appears more convenient than that employed earlier for amino acid IIa, which was obtained from phenylacetic acid through the α-bromo acid bromide.[4]

The intermediate aminoamides were prepared with concentrated sulfuric acid under milder conditions. As these compounds are relatively insoluble, they were readily isolated free from any amino acid that might have been formed. Aminoamide IIIc was obtained in better yield with polyphosphoric acid, which is specific for amide formation.[5]

In Table I are listed some infrared bands. The amino acids IIa, IIb, and V exhibited absorption bands for bonded O—H at 3.5–4.1 μ, and C=O at 6.1–6.3 μ.[6] The aminoamides IIIa–c and VI exhibited characteristic bands for N—H at 3.0–3.1 μ and C=O at 5.9–6.0 μ.[7] However, the aminonitriles Ia–c and IV exhibited only a very weak band or no absorption band for the nitrile group. Ia gave a very faint peak at 4.51 μ[8] which was insufficient for characterization.

Attempts to alkylate amino acid IIa and aminoamide IIIa through their dianions IIa′ and IIIa′ as described for the alkylations of phenylacetic

(1) Supported by the National Institutes of Health Grant CY-4455(C2).

(2) C. R. Hauser, H. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, **82**, 1786 (1960).

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