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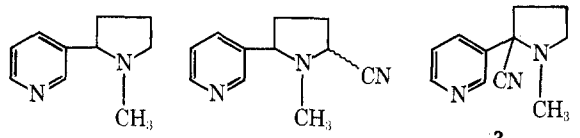
Nicotine Chemistry. 5′-Cyanonicotine

Summary: The synthesis of 5′-cyanonicotine is reported. An attempt to reproduce a literature preparation of this compound led to a mixture of isomeric cyanonicotines in which 2′-cyanonicotine predominated.

Sir: Murphy[1] has recently reported that oxidation of nicotine (1) with mercuric acetate, followed by treatment of the intermediate with potassium cyanide, results in the formation of a cyanonicotine. The product was assigned structure 2 on the basis of its mass and NMR spectra.

Repetition of Murphy's procedure[2] in our laboratory gave a compound which has been unequivocally characterized as 3 based on an independent synthesis of 2 and a detailed spectral analysis of 2 and 3.



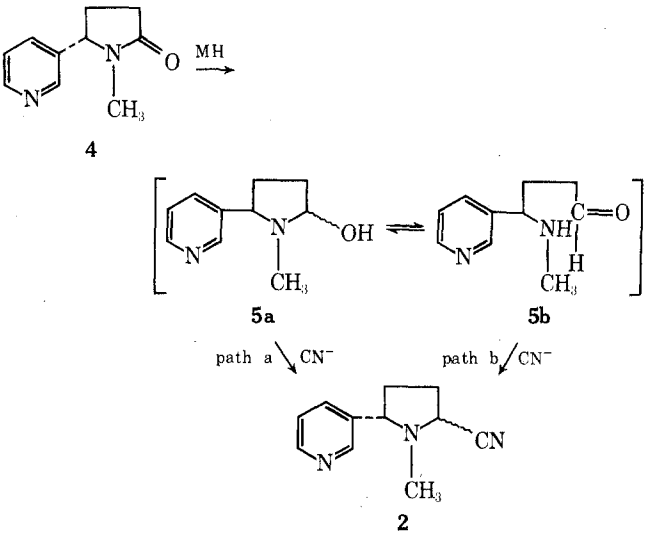
1 2 3

(*S*)-Cotinine (4)[3] was chosen as a logical starting point for the synthesis of 2 in that functionality is already present at the C-5′ position. Since tertiary amides have been reductively cleaved to secondary amines and aldehydes by metal hydrides,[4] introduction of the cyano group at C-5′ was envisaged as proceeding through a cyclic carbinolamine or an acyclic amino aldehyde as shown in Scheme I.[5]

When 4 was treated with 1.6 equiv of a fresh, standardized solution of sodium aluminum hydride[7] in dry tetrahydrofuran, a highly unstable product was isolated which exhibited an intense ir band at 1735 cm^{-1}, typical of a saturated aldehyde. Treatment of the partial reduction product with an excess of aqueous potassium cyanide and ammonium chloride gave an inseparable mixture of (2′*S*)-*cis*- and -*trans*-5′-cyanonicotine (2),[8] isolated in 75% yield (see Scheme I).

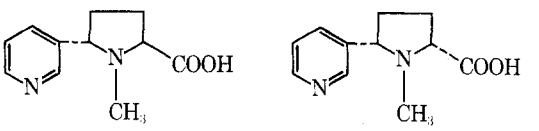
All spectral data for the mixture of the two nitriles were consistent with the assigned structure.[8] Acid hydrolysis of the mixture of nitriles gave a mixture of two nicotine-5′-carboxylic acids in a 2:1 ratio which were subsequently separated by fractional crystallization. The major isomer was

Scheme I



4 5a 5b 2

determined to be (2′*S*)-*trans*-nicotine-5′-carboxylic acid (6) based on the low field signal of the 5′ proton in its ^1H NMR spectrum,[9] while the minor isomer was assigned the cis configuration (7). In addition, ir and ^1H NMR spectra of



6 7

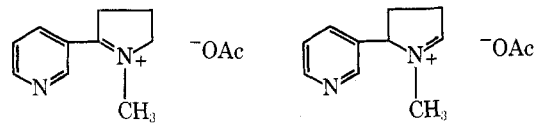
6 were identical with those of a racemic nicotine-5′-carboxylic acid of previously unassigned stereochemistry which was prepared by independent synthesis.[10]

The preparation of authentic 5′-cyanonicotine allowed us to investigate the structure of the product obtained from Murphy's procedure. Nicotine was treated with mercuric acetate in acetic acid. After addition of potassium cyanide to the neutralized (pH 7.0) solution, the components of the product mixture were found to be cotinine (~50%)[12] (4), unreacted 1, and a small amount of a nitrile. The crude product was distilled to give a 5% yield of an unstable oil which displayed a weak band at 2300 cm^{-1} in the ir. The ^1H NMR spectrum of the product, assigned structure 3, was significantly different from the spectrum of 2. The mass spectrum of 2 displayed a prominent molecular ion at *m/e* 187 and a base peak at *m/e* 109, whereas the spectrum of 3 had a barely detectable molecular ion, with a base peak at *m/e* 159.

The ^{13}C NMR spectrum of 3 upon SFOR decoupling is split into one quartet, three triplets, and a singlet [43.0 (q), 21.1, 36.2, and 53.7 (t), and 69.6 ppm (s)]. This pattern is consistent with an *N*-methylpyrrolidine containing a single tetrasubstituted carbon atom. The ^{13}C NMR spectrum of 2 shows a pair of peaks for each of the five saturated carbon atoms. The SFOR-decoupled spectrum displays a pair of quartets (36.5 and 38.1 ppm), a pair of triplets and a single triplet (33.6, 34.5, and 28.9 ppm), and two pairs of doublets (57.0 and 56.1 and 65.6 and 68.3 ppm) consistent with two isomeric *N*-methylpyrrolidines each containing two monosubstituted carbon atoms. Gas chromatography of 3 shows the presence of a small amount of 2 (~10%).[13]

The formation of 2′-cyanonicotine in our laboratory from the mercuric acetate dehydrogenation of nicotine establishes that its precursor is 8. This is consistent with the generalization[14] that mercuric acetate dehydrogenation of α-substituted cyclic amines results in the formation of the more substituted imminium salt. On the other hand, the

formation of cotinine, as well as varying amounts of 5′-cyanonicotine, probably occurs by way of **9**. If this is indeed



8 **9**

the case, then not only must one be concerned with the apparent preferential formation of **9**, but also with its subsequent facile oxidation.

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References and Notes

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(12) Dr. Murphy has informed us that he also obtained a significant amount of cotinine.
(13) A comparison of spectral data obtained by Dr. Murphy from the cyanonicotine which he obtained from treatment of nicotine with mercuric acetate with our spectral data proved conclusively that he did indeed obtain 5′-cyanonicotine. The discrepancies between these results may be due to slight differences in the experimental procedures since we have noted that the ratio of **3**:**2** is a function of the pH of the solution to which cyanide is added.
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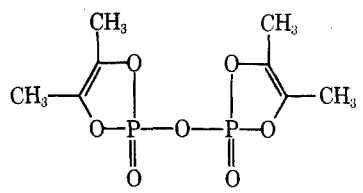
One-Flask Phosphorylative Coupling of Two Different Alcohols

Summary. Aryl (1,2-dimethylethenylenedioxy) phosphates are effective reagents for the "one-flask" conversion of two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, which are readily hydrolyzed to unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$.

Sir: We would like to describe experiments of practical and theoretical importance for the synthesis of unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$, and for studies on the mechanism and the biological functions of phosphate esters.

Crystalline aryl (1,2-dimethylethenylenedioxy) phosphates, e.g., the known[1,2] *p*-nitrophenyl ester (**2**) and the new[3] pentafluorophenyl ester (**3**, mp 54–56°; $\delta_{^{31}P}$ −8.0 ppm, τ 7.98, both in $CDCl_3$) are obtained in 90–95% yield from the reaction of phenols with oxybis(1,2-dimethylethenylenedioxyphosphoryl)[1,2] (**1**).



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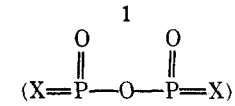

The reagents, X=P(O)OAr [**2** (Ar = p-$NO_2C_6H_4$) and **3** (Ar = C_6F_5)], are capable of converting two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, without isolation of intermediates ("one-flask" reactions), in high yields by simple isolation techniques and within short periods of time; see Table I. The hydrolysis has already been described.[2]

$$(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3] + HO^- \rightarrow (R^1O)(R^2O)P(O)O^- + CH_3COCH(CH_3)OH$$

The synthesis consists of two steps (1 and 2), both of which are effectively catalyzed by salts of the phenols, e.g., $ArO^-(C_2H_5)_3NH^+$. The catalyst is generated by the introduction of the amine together with the first alcohol, R^1OH, since the phenol is a by-product of the reaction 1.

Table I
One-Flask Phosphorylative Coupling of Two Different Alcohols

No.	R^1 in R^1OH	R^2 in R^2OH	Yield of triester,[b] %
		X=P(O)OC$_6$H$_4$NO$_2$-*p*[a]	
1	c-C_5H_9	*i*-C_4H_9	93
2	c-C_5H_9	$C_6H_5CH_2$	91
3	c-C_5H_9	CH_2=$C(CH_3)CH_2CH_2$	93[c]
		X=P(O)OC$_6$F$_5$[d]	
4	c-C_5H_9	$BrCH_2CH_2$	97
5	$(CH_3)_3CCH_2$	*i*-C_4H_9	98[e]
6	c-C_5H_9	*i*-C_4H_9	90

[a] A dichloromethane solution containing R^1OH (1 mol equiv) and triethylamine (1 mol equiv) was added dropwise in 5 min to a stirred dichloromethane solution of X=P(O)$C_6H_4NO_2$-*p* (1 mol equiv; 0.4–0.6 *M*) at 25°. After 15–30 min at 25°, a dichloromethane solution of R^2OH was added dropwise in ~5 min to X=P(O)OR^1. The reaction was allowed to proceed for ~1–2 hr at 25° (0.3–0.5 *M*). The solution was diluted with dichloromethane to ~0.2 *M* and was repeatedly extracted with cold, dilute aqueous alkali (Na_2CO_3 or NaOH) to remove the *p*-nitrophenol. The organic layer was washed first with 5% hydrochloric acid and then with water, dried over Na_2SO_4, filtered, and evaporated in vacuo to yield the dialkylacetoinyl phosphate. The triester was hydrolyzed to the dialkyl phosphate by known procedures.[2] [b] Crude triester, based on R^1OH. Purity >98% based on ^1H NMR spectrometry (in $CDCl_3$) and on conversion to amine salt of diester.[2] [c] Triester purified by short-path distillation (at 0.05 mm, bath temp ~100°), yield 81%. [d] As in the previous procedure (footnote *a*) except using X=P(O)OC_6F_5. The reaction of eq 2 was allowed to proceed for ~5 hr at 25° (0.5 *M*). [e] Triester purified by short-path distillation (at 0.10 mm, bath temp ~95°), yield 94%.