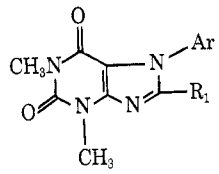
TABLE I
7-ARYLTHEOPHYLLINES[c]

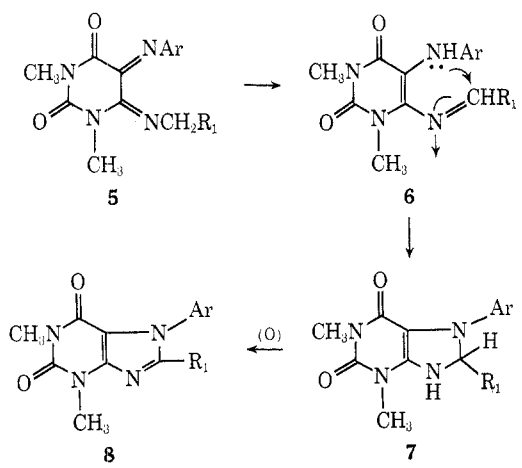


Registry no.	R_1	Ar	Yield, %	Recrystn solvent	Mp, °C[a]
960-61-2	H	C_6H_5	31	Ethanol	195.5[b]
36748-65-9	H	*p*-ClC_6H_4	48	1-Propanol	245.2
36748-66-0	CH_3	C_6H_5	38	Methanol	235.0
36748-67-1	CH_3	*p*-ClC_6H_4	40	Methanol	250.5
36748-68-2	C_6H_5	C_6H_5	48	Ethanol	221.3
36748-69-3	C_6H_5	*p*-ClC_6H_4	70	1-Propanol	267.6

[a] All melting points are corrected and were determined on a Mettler FP-1 apparatus. [b] Lit. mp 193–194.5° (ref 5). [c] Satisfactory analytical values (±0.3% in C, H, N) were reported for all compounds in the table: Ed.

final 7-aryltheophylline.[6] Results are summarized in Table I.

We suggest that this new purine synthesis involves the intermediacy of a 5-hydroxylamino derivative (**2**, R = CH_3, C_2H_5, $CH_2C_6H_5$) which suffers dehydration in the acetic anhydride medium to give the diimine **5**. Prototropic rearrangement would then give the monoimine **6**, which is ideally disposed for intramolecular cyclization to **7**. Subsequent dehydrogenation by excess arylnitroso compound would then lead to the 7-aryltheophylline **8** and an arylhydroxylamine. Since



azoxybenzene (and 4,4′-dichloroazoxybenzene) were also isolated from reactions involving nitrosobenzene and *p*-chloronitrosobenzene, respectively, a further reaction of the hydroxylamine with unreacted arylnitroso compound must occur, indicating the ultimate participation of 3 mol of the latter. Utilization of this stoichiometry significantly improved the yields of the 7-aryltheophyllines.

Experimental Section

7-Aryltheophyllines. General Procedure.—A solution of 0.01 mol of the 1,3-dimethyl-6-alkylaminouracil[7] and 0.03 mol of nitrosobenzene (or *p*-chloronitrosobenzene) in 30 ml of acetic anhydride was heated under gentle reflux for 30 min and poured into 500 ml of water, and the resulting solution was neutralized with aqueous ammonia[8] and allowed to stand overnight at room temperature. The yellow solid which had separated was collected by filtration, washed well with ether to remove coprecipitated azoxybenzene (or 4,4′-dichloroazoxybenzene), and recrystallized as specified in Table I.

(6) For other purine syntheses in which the α-C atom of a 6-alkylamino substituent becomes C-8 in the final product, see, for example, (a) W. Pfleiderer and H.-U. Blank, *Angew. Chem., Int. Ed. Engl.*, **5**, 666 (1966); (b) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **691**, 142 (1966).

(7) 1,3-Dimethyl-6-methylaminouracil and 1,3-dimethyl-6-ethylaminouracil: W. Pfleiderer and K.-H. Schundehutte, *Justus Liebigs Ann. Chem.*, **612**, 158 (1958). 1,3-Dimethyl-6-benzylaminouracil: H. Bredereck, H. Herlinger, and W. Resemann, *Chem. Ber.*, **93**, 236 (1960).

(8) In the condensation of 1,3-dimethyl-6-methylaminouracil with nitrosobenzene there was no precipitate at this stage; the alkaline solution was extracted with ether and the ether extracts were evaporated to a small volume and cooled to give 7-phenyltheophylline.

Synthesis of Myosmine and Nornicotine, Using an Acyl Carbanion Equivalent as an Intermediate[1a]

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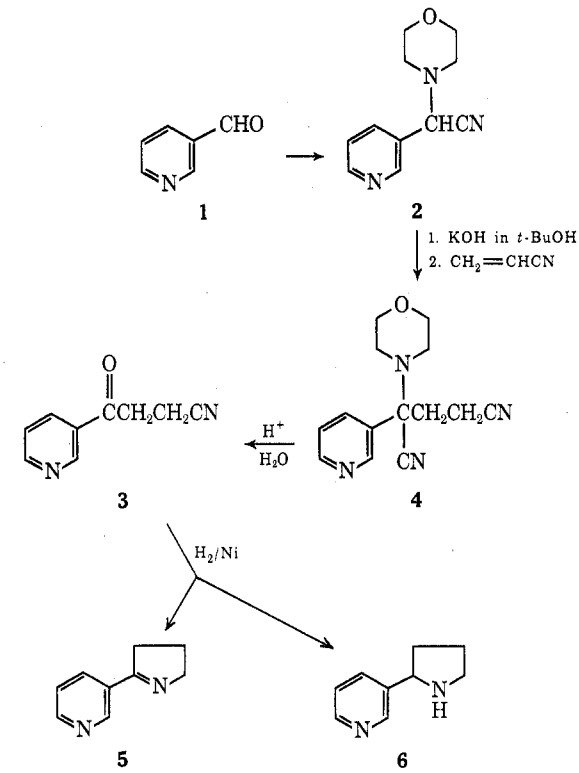
Myosmine (**5**) has been isolated from tobacco smoke and is a minor component of the alkaloids of *Nicotiana tabacum*.[2] It has been synthesized by several methods[3] and on reduction affords nornicotine (**6**).



For our studies on the metabolism of the tobacco alkaloids we required a synthesis of these alkaloids

(1) (a) This investigation was supported by Research Grant GM-13246 from the National Institutes of Health; (b) Contribution No. 122 from this laboratory.

(2) R. L. Stedman, *Chem. Rev.*, **68**, 153 (1968).

(3) (a) E. Späth and L. Mamoli, *Ber.*, **69**, 757 (1936); (b) C. F. Woodward, A. Eisner, and P. G. Haines, *J. Amer. Chem. Soc.*, **66**, 911 (1944); (c) M. L. Stein and A. Burger, *ibid.*, **79**, 154 (1957); (d) R. V. Stevens, M. C. Ellis, and M. P. Wentland, *ibid.*, **90**, 5576 (1968); (e) B. P. Mundy, B. R. Larsen, L. F. McKenzie, and G. Braden, *J. Org. Chem.*, **37**, 1635 (1972).

which would enable us to introduce an appropriate isotope at specific positions.

The key step in our four-step synthesis from pyridine-3-aldehyde (**1**) is the 1,4 addition of the anion of α-morpholino-α-(3-pyridyl)acetonitrile (**2**), an acyl-carbanion equivalent,[4] to acrylonitrile, affording γ-cyano-γ-morpholino-γ-(3-pyridyl)butyronitrile (**4**). The scope of this novel addition is being investigated. Compound **2** was obtained by the addition of aqueous potassium cyanide to the iminium salt formed by heating pyridine-3-aldehyde with morpholine perchlorate in morpholine.[5] Hydrolysis of **4** with aqueous acetic acid[6] yielded 3-cyano-1-(3-pyridyl)propan-1-one (**3**). Hydrogenation of this β-ketonitrile in ethanolic ammonia in the presence of Raney nickel at 3-atm pressure for 24 hr yielded a mixture of myosmine (30%) and nornicotine (60%), separated by preparative thin layer chromatography. The overall yield of the combined alkaloids from pyridine-3-aldehyde was 67%.

Experimental Section

Melting points are corrected. Microanalyses were carried out by Clark Microanalytical Laboratories, Urbana, Ill. Mass spectra were determined on an Hitachi Perkin-Elmer RMU-6D mass spectrometer.

α-Morpholino-α-(3-pyridyl)acetonitrile (2).—Pyridine-3-aldehyde (Aldrich Chemical Co.) (6.95 g) was added to a solution of morpholine perchlorate (13.3 g) in morpholine (64 ml) and the mixture was heated at 80° for 1 hr. Potassium cyanide (4.5 g), dissolved in a minimum amount of water, was added and the mixture was heated at 100° for an additional hour. The cooled reaction mixture was added to aqueous potassium carbonate (10%) and extracted with $CHCl_3$ (4 × 50 ml). The combined extract was washed with aqueous $NaHSO_3$ and then dried ($MgSO_4$). Evaporation yielded **2** as a colorless oil (12.4 g, 92%) which crystallized on standing. Crystallization from cyclohexane afforded **2** as colorless plates, mp 53–54.5°, mass spectrum *m/e* 203 (parent peak).

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.62; H, 6.20; N, 20.33.

γ-Cyano-γ-morpholino-γ-(3-pyridyl)butyronitrile (4).—Acrylonitrile (0.61 g) dissolved in *tert*-butyl alcohol (30 ml) was added slowly (during 30 min) to a stirred solution of **2** (1.89 g) in *tert*-butyl alcohol (100 ml) which contained 11 drops of a methanolic solution of KOH (30%), the reaction being carried out at room temperature under N_2. After stirring for an additional 5 min the reaction mixture was diluted with an equal volume of water and extracted with $CHCl_3$ (4 × 50 ml). The residue obtained on evaporation of the dried ($MgSO_4$) extract was crystallized from a mixture of $CHCl_3$ and Et_2O, affording **4** as colorless prisms (2.14 g, 90%), mp 120–121°, mass spectrum *m/e* 256 (parent peak), 202 (M − CH_2CH_2CN).

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.21; H, 6.46; N, 21.70.

3-Cyano-1-(3-pyridyl)propan-1-one (3).—Compound **4** (1.70 g) was dissolved in a mixture of acetic acid (10 ml), water (5 ml), and tetrahydrofuran (1.5 ml) and warmed at 53° for 24 hr. The reaction mixture was made basic with solid K_2CO_3 and extracted with $CHCl_3$. The residue obtained on evaporation of the dried ($MgSO_4$) extract was crystallized from Et_2O, affording the β-ketonitrile **3** as colorless plates (0.96 g, 90%), mp 66–67°.

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.80; H, 5.13; N, 17.53.

Myosmine (5) and Nornicotine (6).—The β-ketonitrile **3** (2.31 g), dissolved in ethanol (200 ml) which had previously been saturated with ammonia, was hydrogenated at room temperature in the presence of Raney nickel (one spoonfull) at 3-atm pressure for 24 hr. The filtered mixture was acidified with HCl and evaporated to dryness *in vacuo*. The residue was made basic with aqueous K_2CO_3 and extracted with CH_2Cl_2. The liquid obtained on evaporation of the dried ($MgSO_4$) extract was subjected to preparative tlc on silica gel PF-254 (Merck), developing with the mixture of $CHCl_3$, ethanol, and concentrated NH_3 (85:14:1). The higher zone (R_f 0.63) on extraction with $CHCl_3$ afforded myosmine (0.64 g, 30%), identical (nmr, ir, tlc) with an authentic specimen. It afforded a dipicrate, mp 183–185° (lit.[3a] mp 184–185°). The lower zone (R_f 0.20) yielded *dl*-nornicotine (1.29 g, 60%), identical with an authentic specimen.

By reducing the duration of the hydrogenation the yield of myosmine was increased at the expense of the nornicotine.

Registry No.—**2**, 36740-09-7; **3**, 36740-10-0; **4**, 36740-11-1; **5**, 532-12-7; **6**, 5746-86-1.

(4) (a) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971), describe the use of protected aldehyde cyanohydrins for the synthesis of ketones; (b) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969), has reviewed other acyl carbanion equivalents.

(5) D. J. Bennett, G. W. Kirby, and V. A. Moss, *J. Chem. Soc. C*, 2049 (1970), prepared α-aryl-α-morpholinoacetonitriles by this method, and utilized them for the synthesis of [*formyl*-^2H]-labeled aldehydes by quenching the carbanions, generated from these nitriles with base, with deuterium oxide, followed by acid hydrolysis.

(6) Hydrolysis of **4** with hydrochloric acid resulted in the formation of 4-(3-pyridyl)-4-oxobutanoic acid.

An Improved Synthesis of Arylacetylenes

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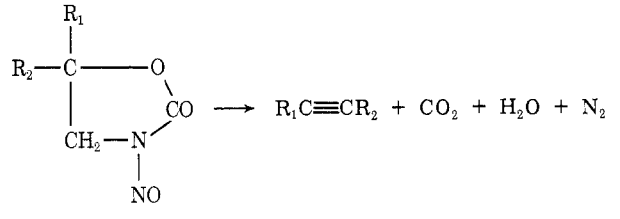
Studies of the alkaline decomposition of the readily prepared[1] 5,5-disubstituted 3-nitroso-2-oxazolidones (**1**)



$R_1 = C_6H_5$; $R_2 = H$
$R_1 = C_6H_5$; $R_2 = CH_3$
$R_1 = R_2 = C_6H_5$
$R_1 = C_6H_5CH_2$; $R_2 = CH_3$

have provided preparative pathways to rather elusive organic structures, *i.e.*, vinyl ethers,[2] vinylsilanes,[3] and vinyl halides.[3] Newman[1] has previously reported obtaining mixtures of acetylenes and carbonyl compounds in a ratio of about 2:1 from the methanolic KOH decompositions of **1a–c**. We wish to report that butylamine in ether quantitatively converts **1a**, **1b**, or **1c** to phenylacetylene, 1-phenylpropyne, and diphenylacetylene, respectively. When an aryl ring is not present in the 5 position of the nitroso oxazolidone, as in **1d**, little acetylenic product is obtained (less than 4%), and a mixture of carbonyl compounds is produced.[4] That this reaction provides an excellent general preparative route to arylacetylenes is illustrated in the following papers.[5,6]

(1) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951).

(2) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).

(3) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **91**, 5678 (1969).

(4) Newman[1] has observed the same results with various 5,5-dialkyl-substituted nitroso oxazolidones.

(5) M. S. Newman and L. F. Lee, *J. Org. Chem.*, **37**, 4468 (1972).

(6) T. B. Patrick, J. M. Disher, and W. J. Probst, *ibid.*, **37**, 4467 (1972).