

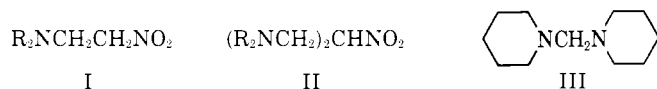
Synthesis of 1,3-Dipyrrolidino-2-nitropropane

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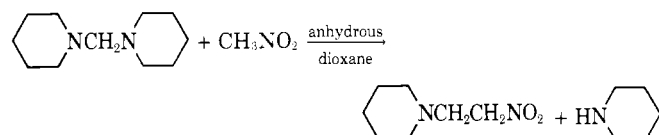
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Dipyrrolidinomethane has been prepared by the reaction of pyrrolidine and formaldehyde. 1,3-Dipyrrolidino-2-nitropropane has been prepared by the Mannich reaction of pyrrolidine, formaldehyde, and nitromethane.

Attempts to prepare *N*-(2-nitroethyl)amines (I) by



Mannich reactions employing dialkylamine, formaldehyde, and nitromethane have invariably led to bis(*N,N*-dialkylaminomethyl)nitromethanes (II) (1, 2). Recently, it was discovered (3) that *N*-(2-nitroethyl)piperidine could be prepared by employing dipiperidino methane (III), under anhydrous conditions, in place of piperidine and formaldehyde:



Our present study of this reaction shows that it is not a general method of preparing the monoalkylated products (I). Even under the above conditions, only the dialkylation products (II) were obtained. Polarographic analysis of reaction mixtures showed no *N*-(2-nitroethyl)di-*n*-propylamine, *N*-(2-nitroethyl)pyrrolidine, or *N*-(2-nitroethyl)morpholine, but that a significant amount of *N*-(2-nitroethyl)-*N*-methylaniline was probably present.

Two new compounds were prepared: dipyrrolidinomethane and 1,3-dipyrrolidino-2-nitropropane.

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EXPERIMENTAL

Dipyrrolidinomethane. One mole of 40% formalin (75 grams) (U.S.P. from Fisher Scientific Co.) was added over a period of 1 hr to 2 moles of pyrrolidine (142 grams) (Matheson, Coleman, and Bell). After a cooling to room temperature, the organic layer was separated, the water layer was salted out with K_2CO_3 , and the combined organic layers were dried—first over $MgSO_4$, then with CaO . Fractional distillation under vacuum yielded 82 grams (55%) of a colorless oil: bp $60^\circ C$ (3.5 mm Hg). Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76; N, 18.17. Found: C, 69.88; H, 11.92; N, 18.27.

1,3-Dipyrrolidino-2-nitropropane. One mole (71 grams) of pyrrolidine was mixed with 0.5 mole (37.5 grams) of formalin. To this mixture was added 0.25 mole (15.3 grams) of nitromethane (redistilled, bp $101-102^\circ C$). After several minutes, a light tan precipitate began to form. The solid 1,3-dipyrrolidino-2-nitropropane was filtered from the reaction mixture and recrystallized from methanol: mp $66-66.5^\circ C$, 20.8 grams (77.4%). Anal. Calcd. for $C_{11}H_{22}N_3O_2$: C, 58.14; H, 9.25; N, 18.50. Found: C, 57.91; H, 9.37; N, 18.53.

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Studies on Ultraviolet Absorption Spectra and Taste of Substituted Benzonitriles

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Regarding the relationship between sweet taste and chemical structure, one of the authors obtained conclusive evidence of the relationship of ultraviolet spectroscopic studies to some dulcin derivatives (18).

Ferguson and Childers (5), by studying the ultraviolet absorption spectra of substituted *m*-nitroanilines, found that some intense sweetness is associated with flat-shaped mole-

cules whose charge distribution is like that found in *p*-disubstituted benzene. This is in accordance with the tentative resonance theory of sweet taste in aromatic molecules (17).

The present paper is primarily concerned with distinguishing the types of sweetness in the various substituted benzonitriles (with a hydrogen free "saccharophore" group, CN), as an approach to elucidate the correlation between the molecular electronic state of those compounds and sweetness.

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Ultraviolet spectroscopic studies of various substituted benzonitriles have been made with respect to the spectral shifts and solvent effects of the compounds, which concern the changes in electronic state of the matrix compound as a measure of the change of the sweetness. This was accomplished by introducing various functional groups. The relationship between sweet taste and the substituents in substituted phenylcyano systems has been studied on the basis of the $\Delta\lambda_K$ vs σ_p diagram as well as the $\Delta\lambda_K$ vs $|\sigma_R^0|$ diagram.

EXPERIMENTAL

The studies can each be broken down into four procedural phases as follows: Phase I was the preparation of benzonitrile derivatives; Phase II involved the sweetness test on these compounds; Phase III concerned noting the changes in the electronic state of the benzonitrile molecule due to the substitution by their functional groups and interaction with solvent molecules by means of the ultraviolet spectroscopic studies. Phase IV involved correlating the characteristic sweetness of these derivatives with the substitution effects on the basis of Hammett's and Taft's parameters as a means of molecular classification. The taste sense and the data of the uv spectra of the various *p*-substituted benzonitriles are given in Table I and, together with those of the ortho- and meta-isomers, in Table II. The taste data were obtained by tests with the specimens both in the solid and liquid states, since the

substituted benzonitriles are, in general, only slightly soluble in water. In the particular system of the halogen derivatives, the sweet taste decreases in the order: F > Cl > Br > I—the iodine derivative being almost tasteless. This is in agreement with the general empirical rule that the taste of the compound is displaced toward tastelessness or bitter taste with increasing molecular weight (12, 16). This displacement toward tastelessness is at least partially related to decreasing solubility. The fact that sweetness decreases in the order of substituents: CH₃ > OCH₃ > Cl (Table I) can therefore be interpreted in terms of this general rule.

The uv spectra of benzonitrile observed in various solvents are shown in Figure 1. The strong bands near 220 nm ($\log \epsilon \sim 4$) and the fine structures in the region of 270–280 nm ($\log \epsilon \sim 3$) may be assigned respectively to the ¹L_a- and ¹L_b-bands of the parent substance, benzene (3, 8). In order to investigate the substituent effect on the ¹L_a-bands of the substituted benzonitriles, Figure 2 shows the bathochromic shifts ($\Delta\lambda_K$) of the ¹L_a-bands and the Hammett's constants σ_p (6, 10), and Figure 3 shows those between the ¹L_a-bands and the Taft's constants $|\sigma_R^0|$, which are considered to be related to the resonance effect, (14, 15). As can be seen in Figure 2, the effects of the substituents can be classified into three groups—namely, those of $\sigma_p < 0$, $\sigma_p > 0$, and of halogens. These three categories coincide with the three classified groups in the orientation effect on aromatic electrophilic substitution, where the halogens are intermediate between the two groups with opposite effects of *o*-, *p*-, and *m*-directions. Figure 3 shows that the substituents are also grouped into three categories, although the relationships are not so good as in Figure 2. A detailed discussion based on the molecular orbital calculation of these effects will be left as a recommended future study. However, the substituted phenylcyano systems which exhibit sweet taste are all located on the particular area surrounded by the dotted lines on the $\Delta\lambda_K$ vs. σ_p diagram in Figure 2 as well as on the $\Delta\lambda_K$ vs. $|\sigma_R^0|$ diagram in Figure 3. The sweetness of these

Table I. Ultraviolet Absorption Spectra of Various *p*-Substituted Benzonitriles in Methanolic Solution (Wavelength in nm)

Sample (Taste)	Bp, °C/mm, mp, °C	¹ L _a -band		¹ L _b -band	
		λ_{\max}	Log ϵ	λ_{\max}	Log ϵ
(H ^c)	66.5–67/10	222.5	4.02	270.5	2.57
(pungent)					
CH ₃ ^{a, b}	98–99/19.5	234.0	4.26	268.0	2.84
(intensely sweet)					
C ₂ H ₅	101–102/10	232.5	4.12	272.8	2.68
(sweet)					
OH	(111–112)	248.5	4.27	Shoulder	
(sweetish and burning)					
OCH ₃	125/15	248.0	4.35	Shoulder	
(sweetish)					
OC ₂ H ₅	(57)	248.8	4.34	Shoulder	
(sweet)					
F	(35.5)	225.1	4.13	262.7	2.48
(sweet and pungent)					
Cl ^d	(93–94)	236.5	4.30	270.0	2.66
(faintly sweet)					
Br ^e	(112)	241.0	4.48	275.0	2.74
(faintly sweet)					
I	(126.5–127)	253.4	4.28	Shoulder	
(tasteless)					
NO ₂	(147–148)	258.3	4.20
(tasteless)					
NH ₂	(86)	276.0	4.09
(tasteless)					
N(CH ₃) ₂	(75.5)	294.5	4.44
(tasteless)					
COCH ₃	(62)	247.0	4.37	288.5	3.25
(faintly bitter)					
CHO	(93–94)	231.5	4.14	279.5	2.59
(almost tasteless)					
CN ^f	(223–224)	237.0	4.47	283.0	3.16
(tasteless)					
CO ₂ CH ₃	(64)	238.3	4.52	284.3	3.20
(sweet)					

^a Ref. 3. ^b Ref. 9. ^c Ref. 1. ^d Ref. 13.

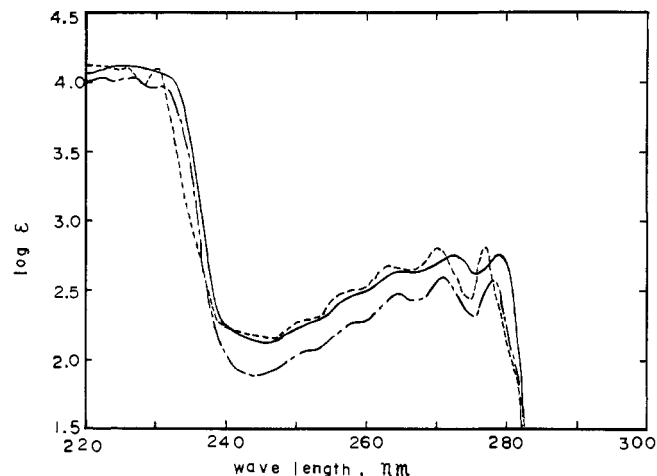


Figure 1. Absorption Spectra of benzonitrile
--- In *n*-hexane ——— In methanol - · - · In water

Table II. Ultraviolet Absorption Spectra of Some Substituted Benzonitriles in *n*-Hexane, Methanol and Aqueous Solution (Wavelength in nm)

Sample (Taste)	Bp, °C/mm (mp, °C)	Solvent	¹ L _a -band		¹ L _b -band	
			λ _{max}	Log ε	λ _{max}	log ε
Benzonitrile (pungent)	66.5-67/10	<i>n</i> -Hexane	221.0	4.12	270.0	2.76
		methanol	222.5	4.02	270.5	2.57
		water ^c	224.0	4.15	271.5	2.95
<i>p</i> -Tolu- (intensely sweet)	98-99/19.5	<i>n</i> -Hexane	230.0	4.26	267.5	3.36
		methanol	234.0	4.26	268.0	2.84
		water ^c	235.0	4.17	268.0	3.57
<i>m</i> -Tolu- (nonsweet)	80.5-81/9	<i>n</i> -Hexane	227.0	4.13	275.0	3.09
		methanol	228.0	4.06	275.5	3.07
		water ^c	229.5	3.98	277.0	3.04
<i>o</i> -Tolu- (cinnamon-like, sweetish)	90.5-91/19	<i>n</i> -Hexane	226.5	4.10	274.5	3.12
		methanol	227.5	4.08	276.0	3.11
		water ^c	229.0	4.00	277.5	3.14
<i>p</i> -Methoxy- (sweet)	125/15	<i>n</i> -Hexane	244.5	4.55	274.5	2.97
		methanol	248.0	4.35
		water ^c	249.5	4.21
<i>m</i> -Methoxy- (almost tasteless)	104-105/5	<i>n</i> -Hexane	228.0	3.97	288.5	3.47
		methanol	230.0	4.01	290.0	3.55
		water ^c	232.0	3.87	293.5	3.46
<i>o</i> -Methoxy- (almost tasteless)	124.5-126/10	<i>n</i> -Hexane	231.0	4.16	289.0	3.72
		methanol	232.0	4.16	295.0	3.80
		water ^c	233.5	3.97	296.5	3.63
<i>p</i> -Chloro- (faintly sweet)	(93-94)	<i>n</i> -Hexane	236.5	4.38	270.0	2.87
		methanol	236.5	4.30	270.0	2.66
		water ^c	238.0	...	270.0	...
<i>m</i> -Chloro- (slightly pungent)	(40)	<i>n</i> -Hexane	228.0	4.04	279.5	2.97
		methanol	228.0	4.05	279.5	3.02
		water ^c	229.0	...	280.5	...
<i>o</i> -Chloro- (slightly sweetish)	(41-42)	<i>n</i> -Hexane	230.0	3.91	279.5	3.07
		methanol	231.0	4.07	280.5	3.17
		water ^c	232.0	...	281.5	...

^a Ref. 3. ^b Ref. 4. ^c Ref. 9.

derivatives in the phenylcyano system decreases along the lines I, II, and III all upward in Figure 2. An exception is observed only with the formyl (CHO) derivative on line III in Figure 2, resulting from the poor solubility of the compound.

As shown in Table II, all the meta-compounds are non-sweet, but the ortho-isomers taste sweetish, and it is a

remarkable fact that the para-derivatives exhibiting sweet taste all show large bathochromic shifts in the ultraviolet spectra (Table I). In Table III are given the bathochromic shifts of the isomers from the parent substance, benzonitrile, where it is seen that the *p*-isomers show larger shifts than the ortho and meta as to the ¹L_a-bands, the order being OCH₃ > Cl > CH₃, which is in harmony with the order

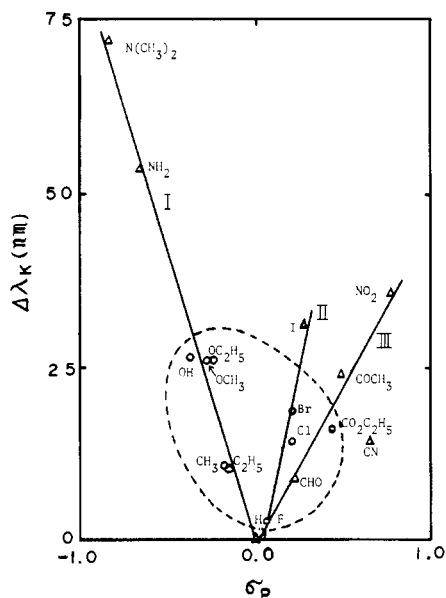


Figure 2. Correlations between the displacements ($\Delta\lambda_K$) of the ¹L_a-band and Hammett's σ_p constant

○ Sweet

△ Nonsweet (standard, benzonitrile, $\lambda_{max} = 222.5$ nm)

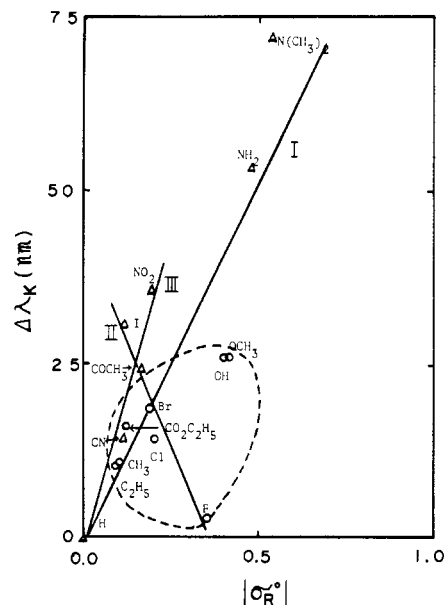


Figure 3. Correlations between the displacements ($\Delta\lambda$) of the ¹L_a-band and Taft's σ_R^0 constant

○ Sweet

△ Nonsweet (standard, benzonitrile, $\lambda_{max} 222.5$ nm)

Table III. Bathochromic Shifts of Substituted Benzonitriles

(From benzonitrile, nm)

Sample	¹ L _a -band			¹ L _b -band		
				<i>n</i> -		
	<i>n</i> -Hexane	Meth-anol	Water	Hex-ane	Meth-anol	Water
Tolunitrile						
para-	9.0	11.5	11.0	-2.5 ^a	-2.5 ^a	-2.5 ^a
meta-	6.0	5.5	5.5	5.0	5.0	5.5
ortho-	5.5	5.0	5.0	4.5	5.5	6.0
Methoxybenzonitrile						
para-	23.5	25.5	25.5	4.5		
meta-	7.0	7.5	8.0	18.5	19.5	22.0
ortho-	10.0	9.5	9.5	19.0	24.5	25.5
Chlorobenzonitrile						
para-	15.5	14.0	14.0	0.0	-0.5 ^a	-1.5 ^a
meta-	7.0	5.5	5.0	9.5	9.0	...
ortho-	9.0	8.5	8.0	9.5	10.0	10.0

^a The negative sign means "hypsochromic shifts."

of $|\sigma_R^0|$. The *p*- and *o*-isomers are capable of conjugation through the phenyl system with the cyano group and, particularly in the *p*-compounds, the contribution of the resonance structure may be largest. This is brought about by the π -electronic transition toward the cyanophenyl from the substituent. As to the solvent effect, as expected, the bathochromic shift due to the $\pi - \pi^*$ transition apparently increases with the increasing polarity of the solvent. Hence, in all the *p*-substituted benzonitriles the contribution of the ionic polar structure is observed, but the sweetness does not necessarily agree with it. Nevertheless, it is suggested by the occurrence of sweet molecules in a limited area in Figure 2 as well as in Figure 3 that the electronic effect of the substituent has a close relationship with the sweetness.

PROCEDURE

Preparation of Materials. Most of the substituted benzonitriles were prepared by Sandmeyer's reaction of corresponding anilines (2). *p*-Fluorobenzonitrile was prepared by dehydration with thionyl chloride from its acid amide synthesized from ethyl *p*-aminobenzoate via *p*-carbethoxybenzene diazonium fluoroborate and *p*-fluorobenzoic acid. *p*-Iodobenzonitrile was prepared by dehydration with thionyl chloride from its acid amide synthesized from *p*-iodobenzoic acid. *p*-(*N,N*-dimethyl)aminobenzonitrile was prepared from its oxime obtained from *p*-(*N,N*-dimethyl)aminobenzaldehyde by dehydrating with acetic anhydride. *p*-Nitrobenzonitrile was obtained from *p*-nitrobenzoic acid by Miller's method (11), *p*-Cyanophenol was prepared by deacetylating *p*-acetoxybenzonitrile obtained from *p*-hydroxybenzaldoxime by the reaction of acetic anhydride with

sodium methoxide in dry methanol. *p*-Cyanacetophenone was prepared from bromoacetophenone by Rosenmund von Braun reaction (7). *p*-Dicyanobenzene was prepared from terephthalic acid by Miller's method (11) with slight modification.

All the samples were purified before use by fractional distillation or by recrystallization from suitable solvents. The identity was confirmed by mp and bp as well as by ir spectra in a KBr disk or in liquid film and those nmr spectra in CCl₄ or CDCl₃ solution. The nmr studies will be published in another paper.

Uv Spectroscopic Studies. The absorption spectra of benzonitrile derivatives were taken in various solvents such as *n*-hexane, methanol, and water. The measurements were carried out at room temperature (20–21°C) in the region ranging from 220–340 nm by means of a Hitachi EPS-II type spectrophotometer.

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