

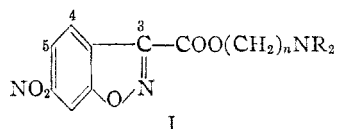
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The Rearrangement of Benzisoxazole-3-carboxylates

BY R. O. CLINTON AND S. C. LASKOWSKI

Dialkylaminoalkyl 6-nitrobenzisoxazole-3-carboxylates, when heated in toluene solution, undergo rearrangement to the corresponding 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles. Similarly, an alkyl 6-nitrobenzisoxazole-3-carboxylate, in the presence of a tertiary amine, forms the corresponding 2-alkoxy-4-nitrobenzonitrile and a quaternary ammonium salt. Dimethylaminoethyl 6-nitrobenzisoxazole-3-carboxylate is exceptional, in that self-alkylation occurs exclusively. The 6-nitrobenzisoxazole-3-carboxamides do not undergo rearrangement. Possible mechanisms for these reactions are discussed, and the products of rearrangement characterized through independent syntheses.

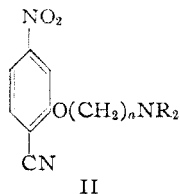
In connection with related studies of basic esters and amides, there arose the problem of preparing a series of dialkylaminoalkyl 6-nitrobenzisoxazole-3-carboxylates, I. Since preliminary experiments had shown that alkyl 6-nitrobenzisoxazole-



3-carboxylates underwent transesterification with great facility, this method was investigated as a means of obtaining the desired compounds. However, initial experiments indicated that under certain conditions anomalous results were obtained. These results are the subject of the present communication.

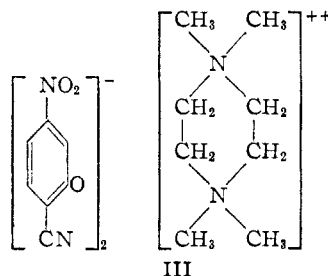
When methyl 6-nitrobenzisoxazole-3-carboxylate (hereinafter abbreviated "MNBC") was allowed to react with a dialkylaminoalkanol in boiling toluene solution for one-half hour, under conditions ensuring the removal of methanol, a high yield of the corresponding basic ester, I, was obtained (see Table I). These esters were very unstable as the free bases (*vide infra*), but quite stable in the form of their salts.

Lengthening the reflux period gave rise to divergent results. It was found that by prolonging the reaction between, *e.g.*, 2-diethylaminoethanol and MNBC in boiling anhydrous toluene to a period of six to ten hours, apparent decomposition ensued and a gas, identified as carbon dioxide, was slowly evolved. From the resulting reaction mixture was isolated, in addition to the corresponding basic ester, I ($n = 2$, $R_2 = (C_2H_5)_2$), a new compound produced by the rearrangement of this ester. Analyses and independent synthesis proved that this new compound was 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile, II ($n = 2$, $R_2 = (C_2H_5)_2$).

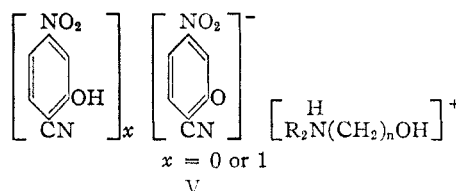
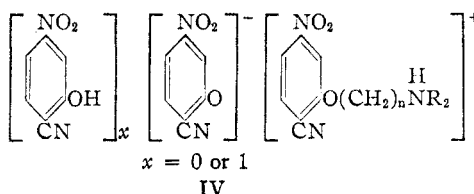


A similar result was obtained when pure 2-diethylaminoethyl 6-nitrobenzisoxazole-3-carboxylate was refluxed in toluene solution under anhydrous conditions. The use of other dialkylaminoalkanols, with the exception of 2-dimethylaminoethanol, also led to the isolation of analogous compounds of type II. The use of 2-dimethylaminoethanol

under these conditions gave only a highly colored salt-like compound, which was shown by degradation experiments and by synthesis to possess the structure III.



When moisture was present during the long-period reaction of a dialkylaminoalkanol with MNBC, or in a boiling toluene solution of I, a number of highly colored reaction products were obtained in addition to I and II. In the majority of cases these were shown to possess structures of type IV or V.



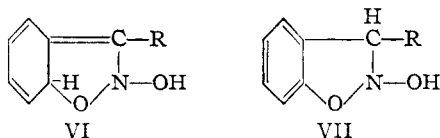
Further, identical compounds were isolated when the pure basic esters, I, were allowed to decompose spontaneously in air at room temperature.

The chemistry of benzisoxazole derivatives has been investigated by Borsche¹ and by Lindemann and co-workers.² These authors have shown that simple benzisoxazoles, when treated with aqueous sodium hydroxide, undergo cleavage to yield the corresponding salicylnitrile or ketoxime. This conversion has been ascribed by Lindemann² to a "tautomeric shift" (if hydrogen or a hydrogen precursor such as carboxyl is present in the 3-position), or to simple addition of the elements of water to the isoxazole ring, as in VI or VII. It is readily apparent

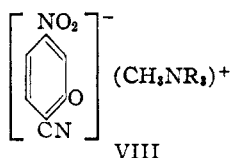
(1) W. Borsche, *Ann.*, **390**, 1 (1912).

(2) H. Lindemann, *et al.*, *ibid.*, **449**, 63 (1926); **451**, 241 (1927); **456**, 284 (1927); **469**, 44 (1929); *J. prakt. Chem.*, **122**, 214, 232 (1929).

that the present results make either explanation untenable.



In a consideration of possible reaction mechanisms for the formation of II from I, several factors were considered. The rate of the rearrangement, and therefore the yield of II from I, was found to be a function of both n and R_2 in I, *e.g.*, the greater the value of n , the slower the rate of rearrangement. Since the rearrangement was independent (except for rate effects) of the value of n in I, it seemed likely that it would also take place with any ester of 6-nitrobenzisoxazole-3-carboxylic acid in the presence of a base. This corollary was experimentally shown to be true. MNBC when refluxed with a tertiary amine in dry toluene solution yielded a mixture of 2-methoxy-4-nitrobenzonitrile and the ammonium phenolate salt VIII. Similar results were obtained with the corresponding ethyl ester, although the rate was much slower.

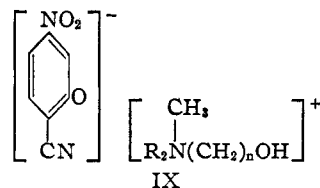


The isolation of VIII indicated that the mechanism of the rearrangement might involve alkylation of the tertiary amino nitrogen by the alkyl moiety of the ester, with subsequent alkylation of the phenolate ion by the quaternary ammonium ion after carbon dioxide elimination. In analogy, Fuson, Corse and Horning³ have shown that the quaternary ammonium salts of aromatic acids give, when heated, high yields of the corresponding alkyl esters. Further, Tarbell and Vaughan⁴ have obtained phenyl allyl ether by the distillation of dimethylphenylallylammonium phenolate.

However, it was shown experimentally that VIII was not an intermediate in the formation of 2-methoxy-4-nitrobenzonitrile. When a toluene suspension of synthetically prepared VIII was refluxed for a considerable period of time, no detectable trace of 2-methoxy-4-nitrobenzonitrile was found; instead VIII was recovered quantitatively. Further, when MNBC was refluxed in toluene solution with *catalytic* amounts of a tertiary amine, the reaction ceased abruptly within a short period of time, as evidenced by cessation of carbon dioxide evolution, and only minute amounts of 2-methoxy-4-nitrobenzonitrile were isolated. Again, it would be expected that if a compound of type VIII was involved in the rearrangement, then similar intermediates, *e.g.*, IX, would be isolable from the reaction between MNBC and a dialkylaminoalkanol. Thus, a mixture of compounds similar to II would be obtained, since the methyl group would be transferred with at least equal facility. The experimental evidence obviates this explanation.

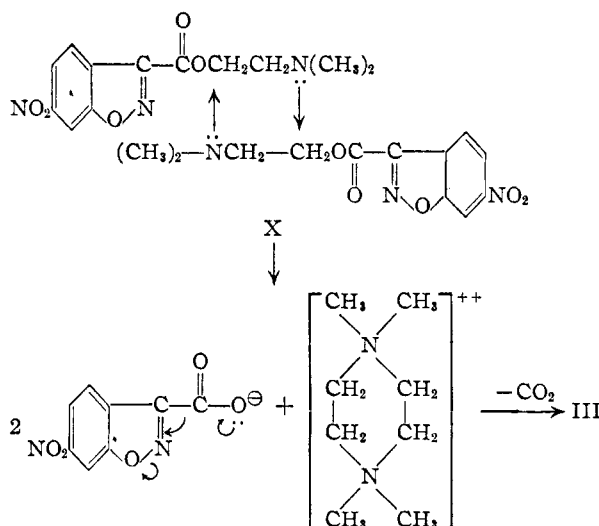
(3) R. C. Fuson, J. Corse and E. C. Horning, *THIS JOURNAL*, **61**, 1290 (1939).

(4) D. S. Tarbell and J. R. Vaughan, *ibid.*, **65**, 231 (1943).



It is thus apparent that two simultaneous reactions occur during the reaction of MNBC with a dialkylaminoalkanol or a tertiary amine. With the dialkylaminoalkanol the alkylation reaction to form compounds of type IX must be very slow or non-existent in comparison with transesterification (and subsequent rearrangement). On the other hand, with an unsubstituted tertiary amine the two reactions become competitive, since the rate of rearrangement of an alkyl group is also very slow.

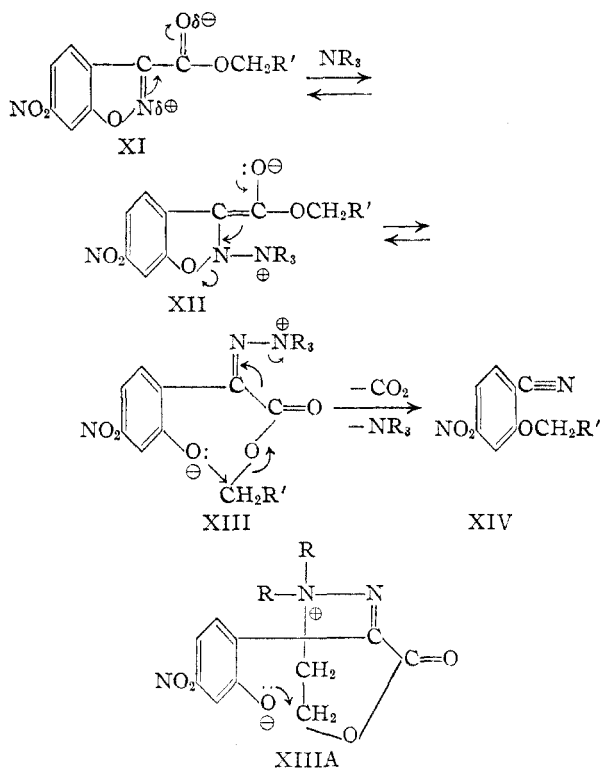
In the special case of 2-dimethylaminoethanol, intermolecular self-alkylation takes place rapidly and exclusively, without rearrangement. A reasonable mechanism is shown in X to III.



A consideration of the above evidence for the reaction between MNBC and dialkylaminoalkanol, other than 2-dimethylaminoethanol, leads to the postulated rearrangement shown in XI-XIV.

The 2-nitrogen of the isoxazole ring, rendered electrophilic by virtue of the polarization indicated in XI, can undergo attack by a tertiary amine (either unsubstituted, as in the reaction of MNBC with triethylamine, or a dialkylaminoalkanol as the ester) to give the product XII. The latter, by means of the electronic shifts shown, yields XIII, which in turn will eliminate carbon dioxide and regenerate the catalyst with production of the isolated compound, XIV. The rearrangement of the alkyl group shown in XIII is thus a simple intramolecular nucleophilic displacement (S_N2 with inversion), which is known to be a base catalyzed reaction. The reaction is therefore strictly analogous to the *intermolecular* alkylation of, *e.g.*, the 2-cyano-5-nitrophenolate ion by a dialkylaminoalkyl chloride. The driving force of the reaction is the cleavage of carbon dioxide from the intermediate XIII.

It seems probable, on the basis of the experimentally observed reaction rates, that with a



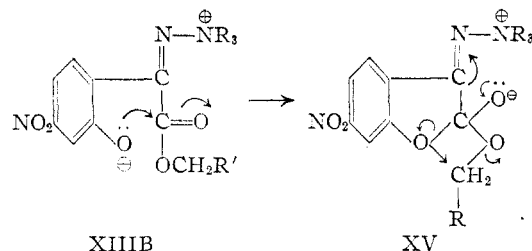
compound such as 2-diethylaminoethyl 6-nitrobenzoxazole-3-carboxylate the base catalysis is *intramolecular*, as shown in XIIIa, (rapid reaction, high yield) while with, *e.g.*, 3-diethylaminopropyl 6-nitrobenzoxazole-3-carboxylate the base catalysis is *intermolecular* (slow reaction, low yield). Additional weight is lent to this hypothesis by the construction of Fisher-Hirschfelder models. These models indicate easy access of the terminal amine grouping to the 2-position of the benzisoxazole nucleus in a 2-dialkylaminoethyl chain and difficult access with a 3-dialkylaminopropyl chain.

The mechanism postulated above does not contradict the evidence of non-alkylation in VIII and experimentally obtained evidence of non-alkylation of the 2-cyano-5-nitrophenolate ion by MNBC or by the electronically similar compound, methyl benzoylformate (although the latter compound will readily alkylate an amine). Some additional evidence might be obtained through the use of, *e.g.*, crotyl 6-nitrobenzoxazole-3-carboxylate which should rearrange with inversion.⁵ Judged, however, by the very low yields obtainable by the rearrangement of ethyl 6-nitrobenzoxazole-3-carboxylate and the absence of rearrangement with hexyl 6-nitrobenzoxazole-3-carboxylate the experiment appears unfeasible.

An alternative mechanism, indicated by XIIIB–XV, is attractive on pictorial grounds since it may be based upon analogous intermediates postulated previously in certain intra- and intermolecular ester-exchange reactions.⁶ However, this mechanism appears untenable, since all of the previously cited examples are acid-catalyzed.

(5) Cf. D. S. Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., Chap. I.

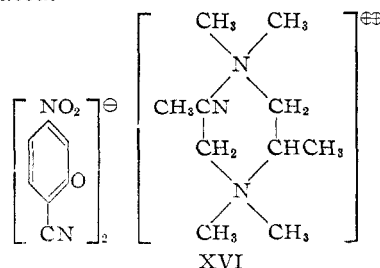
(6) F. J. Sowa, *THIS JOURNAL*, **60**, 654 (1938); S. M. McElvain and D. Kundiger, *ibid.*, **64**, 254 (1942); S. G. Cohen, *ibid.*, **66**, 1395 (1944); W. S. Johnson and A. Goldman, *ibid.*, **67**, 430 (1945).



The synthesis of the 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles, II, was best accomplished by the reaction between sodium 2-cyano-5-nitrophenolate and an ω -dialkylaminoalkyl chloride in absolute alcohol solution. A number of modifications of this method were also used in certain cases, and the series was extended beyond those compounds actually isolated from the rearrangement of I, since they were desired as intermediates for other studies. 2-Hydroxy-4-nitrobenzonitrile, while not as "acidic" as picric acid,⁷ nevertheless did prove capable of reacting with 2-diethylaminoethyl chloride in isopropyl alcohol solution, comparable to the conditions of the Horenstein-Pählicke reaction.⁸ The yield was low, however. On the other hand, when 6-nitrobenzoxazole-3-carboxylic acid was subjected to reaction with 2-diethylaminoethyl chloride in isopropyl alcohol solution a somewhat larger yield of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile was obtained, even though decarboxylation of the acid was very rapid after initial mixing of the components at room temperature.⁹

Special conditions were necessary in the preparation of 2-(2-dimethylaminoethoxy)-4-nitrobenzonitrile, since cyclization of 2-dimethylaminoethyl chloride occurred exclusively in the reaction with sodium 2-cyano-5-nitrophenolate, and only the compound III was isolated. The compound was prepared by the alkylation of potassium 2-cyano-5-nitrophenolate with 2-dimethylaminoethyl chloride in toluene solution, and also by similar alkylation with 2-chloroethyl *p*-toluenesulfonate followed by reaction of the product with dimethylamine.

When 1-dimethylamino-2-chloropropane was allowed to react with sodium 2-cyano-5-nitrophenolate in alcoholic solution, both the desired product corresponding to II and the piperazinium salt XVI were isolated.



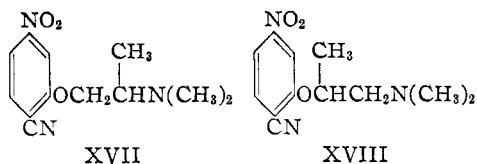
The use of 1-dimethylamino-2-chloropropane under these conditions should result in the two isomers of II, shown in XVII and XVIII, since the

(7) 2-Hydroxy-4-nitrobenzonitrile is readily soluble in aqueous sodium bicarbonate solution.

(8) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(9) 6-Nitrobenzoxazole-3-carboxylic acid undergoes rapid and quantitative decarboxylation when a dry ethyl acetate solution is treated with, *e.g.*, triethylamine.

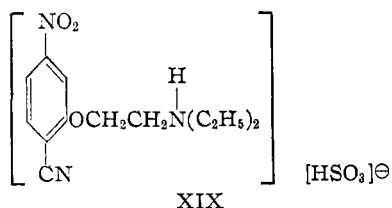
base reacts as though it exists in the intermediate ethyleneimmonium ion in S_N2 -type displacement reactions.¹⁰ The low-melting base which was initially isolated from this reaction gave a single



sharp melting isomer on prolonged recrystallization, but no differentiation between the structures XVII and XVIII has yet been made. The ethyleneimmonium ion is not determinant in the formation of XVI, since either type of cleavage and cyclization would yield the same piperazinium compound.

The pure 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles, II, were photosensitive, readily developing a pink or orange surface-coloration within a few days. They were easily characterized through their crystalline salts and methiodides. These compounds are listed in Table IV.

A unique type of salt was isolated in one case during the investigation of the products from the reaction of MNBC and 2-diethylaminoethanol. A separation of products was attempted through the use of sodium bisulfite solution (utilized as a "weak acid"); with concentrated bisulfite solutions there was obtained a white crystalline salt, probably of structure XIX. The observation that the



compound was white, coupled with the analyses, indicated that the product was not a sulfur dioxide addition product, $R_3N \cdot SO_2$.

The 2-cyano-5-nitrophenolate salts, IV and V, are of especial interest because of their isolation from the decomposition and rearrangement of the basic esters, I, in the presence of moisture, and because of the varying ratios of 2-hydroxy-4-nitrobenzonitrile to base found in these salts. The method of their formation in this reaction requires no discussion. The salts, IV, were synthesized for comparative purposes by the treatment of a pure base, II, with a two mole proportion of pure 2-hydroxy-4-nitrobenzonitrile. The crude salt was recrystallized to a constant melting point. Two types of salts were thus obtained, containing one or two molecules of 2-hydroxy-4-nitrobenzonitrile, respectively (see Table V). It was intriguing in this connection that in two cases the salts V showed a ratio which was the *reverse* of that found in the corresponding salts IV. The second molecule of 2-hydroxy-4-nitrobenzonitrile is probably held through polarization forces as in, *e.g.*, acenaphthene picrate. Apparently the retention of a second

molecule of 2-hydroxy-4-nitrobenzonitrile is governed purely by steric factors, since at present there appears to be no correlation between the pK_b of the terminal tertiary amine grouping and the ratio of phenol to base. It is noteworthy that salts of type III, when treated with an excess of 2-hydroxy-4-nitrobenzonitrile, were recovered unchanged.

The salts III, IV, V, VIII and in general, any amine or ammonium salts of 2-hydroxy-4-nitrobenzonitrile, are highly colored. The monosalts such as IV ($x = 0$) or VIII, and the ammonium salts of type III are without exception more deeply colored than the disalts such as IV ($x = 1$). It was hoped that the spectra of these compounds might be characteristic and that perhaps for this and other reasons, 2-hydroxy-4-nitrobenzonitrile might serve as a new and useful tool in the analytical chemistry of amines. At present, the limited number of amine and ammonium salts prepared provide insufficient evidence from which to draw conclusions. The mono- and disalts of amines all possessed maxima at 265 and 336 $m\mu$ ($\pm 2 m\mu$), and minima at 252 and 302 $m\mu$ ($\pm 2 m\mu$). The disalts alone possessed a further characteristic maximum at 236 $m\mu$ ($\pm 2 m\mu$), and had ϵ values much greater than those of the mono-salts. The piperazinium salts showed no maximum at 336 $m\mu$, but this maximum was present in the methyltriethylammonium salt. In addition, certain of the salts had a distinct maximum at 410 $m\mu$. The spectral characteristics of certain examples of these compounds are shown in Figs. A and B. Those compounds not shown possessed spectra comparable to their analogs.

In contrast to the reaction of MNBC with tertiary amines and with dialkylaminoalkanol, the reaction with primary and secondary amines was straightforward, yielding only the 3-carboxamide derivatives. The 3-carboxamide was obtained exclusively even when a hydroxy group was present in the primary amine (*e.g.*, ethanolamine). The amide bases were very stable, undergoing no alteration on prolonged heating in toluene solution.

A number of attempts were made to reduce the esters I, and also the 3-carboxamides, to the 6-amino-benzisoxazoles. However, the reduction products were extremely unstable, even in the form of their hydrochlorides. Lindemann² has shown that the reduction of a simple benzisoxazole often involves saturation of the 2,3-bond, leading to unstable intermediates.

The 2-alkoxy-4-nitrobenzonitriles and the 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles, II, were converted by reduction to the corresponding 4-amino compounds for pharmacological screening. Further, in order to broaden the types of compounds tested, there were prepared several 4-alkylamino-2-(dialkylaminoalkoxy)-benzonitriles and 4-amino-2-(dialkylaminoalkoxy)-benzonitrile methiodides.

The authors are indebted to Dr. William S. Johnson for a number of stimulating suggestions on the probable course of this rearrangement reaction, and to Dr. F. C. Nachod and staff for the spectra determinations.

(10) W. R. Brode and M. W. Hill, *THIS JOURNAL*, **69**, 724 (1947); P. D. Bartlett, *et al.*, *ibid.*, **69**, 2971, 2977 (1947); S. D. Ross, *ibid.*, **69**, 2982 (1947).

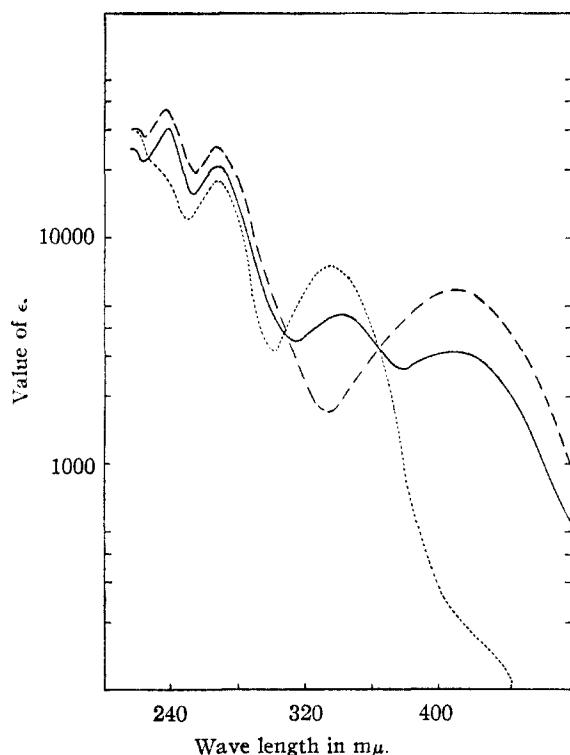


Fig. A.— —, triethylammonium di-(2-cyano-5-nitrophenolate); ---, 2-hydroxy-4-nitrobenzonitrile; . . . , 2-(diethylaminoethoxy)-4-nitrobenzonitrile di-(2-cyano-5-nitrophenolate).

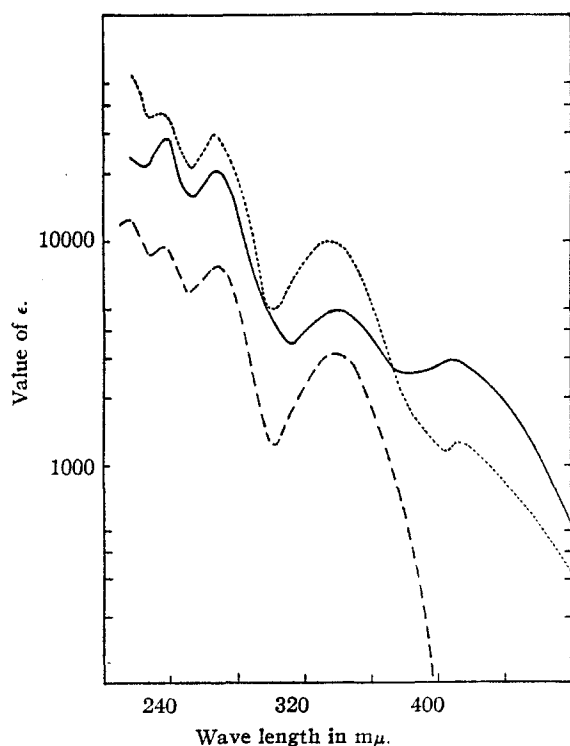


Fig. B.— —, methyltriethylammonium di-(2-cyano-5-nitrophenolate); ---, 1,1,4,4-tetramethylpiperidinium di-(2-cyano-5-nitrophenolate); . . . , 2-(3-(4-morpholinyl)propoxy)-4-nitrobenzonitrile mono-(2-cyano-5-nitrophenolate).

Experimental¹¹

Alkyl 6-Nitrobenzoxazole-3-carboxylates.—The method of Borsche¹ was used for the preparation of 2,4-dinitrophenylacetic acid, on a twenty-mole scale. It was found that the inclusion of 1 to 2 ml. of ethyl alcohol per mole of acid nitrated gave a purer product.¹² The yields varied between 76–84%, and the melting point lay within the range of 161–175°. The semi-pure acid was esterified with methanol by the ethylene dichloride procedure¹³ to give 90–94% yields of pure methyl ester, whereas the Fischer method¹ gave only 70–75% yields. Considerable experimental work was carried out on the large scale conversion of methyl 2,4-dinitrophenylacetate to MNBC. In order to consistently achieve the yield of 85% reported by Borsche¹ it was found necessary to use freshly prepared butyl nitrile and an initial mixing temperature of 40° for the components. The ring closure procedure was also varied by the use of other esters of 2,4-dinitrophenylacetic acid. The propyl, isopropyl and butyl esters, in the respective alcohols as solvents, gave only tarry products; ethyl 2,4-dinitrophenylacetate in ethyl alcohol gave *ca.* 20% of ethyl 6-nitrobenzoxazole-3-carboxylate, pale yellow needles from alcohol, m.p. 99.0–100.0°.

Anal. Calcd. for $C_{10}H_8N_2O_6$: C, 51.07; H, 3.43; N, 14.15. Found: C, 51.07; H, 3.35; N, 14.64; N, 12.15.

A mixture of 40 g. of MNBC, 300 ml. of anhydrous ethyl alcohol and 2 ml. of triethylamine was boiled gently for 20 minutes. The clear solution was diluted while hot with an equal volume of water, cooled, filtered, and the product was washed with water. The resulting material, after drying, was again treated with anhydrous ethyl alcohol and triethylamine as before. There was thus obtained a nearly quantitative yield of ethyl 6-nitrobenzoxazole-3-carboxylate, m.p. and mixed m.p. 99.0–100.0°.

Anal. Found: C, 51.27; H, 3.33; N, 12.13.

A similar reaction, carried out between MNBC, *n*-hexanol and triethylamine catalyst, gave a high yield of *n*-hexyl 6-nitrobenzoxazole-3-carboxylate, waxy plates from ethyl acetate–Skellysolve B, m.p. 60.0–62.0°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 57.53; H, 5.17; N, 9.59. Found: C, 57.00; H, 5.13; N, 9.81.

Dialkylaminoalkyl 6-Nitrobenzoxazole-3-carboxylates. A mixture of 44.4 g. (0.2 mole) of MNBC, 0.22 mole of the redistilled dialkylaminoalkanol and 350 ml. of dry toluene was distilled slowly through a 14" vacuum-jacketed Vigreux column surmounted by a total-reflux variable take-off distillation head. During one-half hour 12 to 16 ml. of distillate was collected; the final distillate temperature was 105°. The pale yellow-brown still residue was decolorized and the toluene was removed *in vacuo*. The residue was dissolved in ethyl acetate and the solution was treated with an excess of 20% ethereal hydrogen chloride. The precipitated white solid was recrystallized from alcohol or isopropyl alcohol; the yields of the pure basic ester hydrochlorides were 65–75%. These compounds are listed in Table I.

A small portion of the pure hydrochloride was dissolved in ice-water and the solution was treated with an excess of cold, saturated sodium bicarbonate solution. The precipitated oily or crystalline base was extracted into cold ethyl acetate, the extract dried, and to the extract was added an excess of a saturated solution of picric acid in absolute alcohol. The precipitated yellow or canary-yellow picrate was recrystallized to constant melting point from glacial acetic acid. The picrates are listed in Table I.

2-Hydroxy-4-nitrobenzonitrile.—The hydrolysis of MNBC with 4% sodium hydroxide solution at 65° according to Borsche¹ gave 70–80% yields of product. The compound crystallized from methanol as a solvate, losing methanol at

(11) All melting points are corrected. They were determined in a modified Hershberg apparatus using total immersion N.B.S. calibrated thermometers. The sample was immersed 15° below the melting point, 3° rise per minute. The analyses were done by Mr. M. E. Auerbach and staff.

(12) Observation of Mr. B. F. Tullar of these laboratories.

(13) R. O. Clinton and S. C. Laskowski, *THIS JOURNAL*, **70**, 3135 (1948).

(14) Nitro nitrogen, by titration with standard titanous chloride in glacial acetic acid solution.

(15) No reduction of the 2,3-double bond occurs in this case; *i.e.*, this bond is not similar to an oxime double bond.

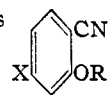
TABLE I
 DIALKYLAMINOALKYL 6-NITROBENZISOXAZOLE-3-CARBOXYLATES

DIALKYLAMINOALKYL 6-NITROBENZISOXAZOLE-3-CARBOXYLATES

n	R ₂	M.p., °C.	Formula	Hydrochloride				M.p., °C.	Picrate				
				Analyses, %		Analyses, %			Analyses, %		Analyses, %		
				Chlorine	Nitrogen ^a	Chlorine	Nitrogen ^a		Nitrogen ^b	Nitrogen ^c	Nitrogen ^b	Nitrogen ^c	
				Calcd.	Found	Calcd.	Found		Calcd.	Found	Calcd.	Found	
2	(CH ₃) ₂	172.0–173.0°	C ₁₂ H ₁₄ ClN ₃ O ₅	11.23	11.22	d, e	d, e	194.0–195.0°	2.76	2.81	11.02	11.04	
2	(C ₂ H ₅) ₂	151.8–153.0°	C ₁₄ H ₁₈ ClN ₃ O ₅ ^f	10.31	10.32	4.07	4.04	160.6–161.6°	2.61	2.62	10.44	10.58	
3	(C ₂ H ₅) ₂	151.5–151.8	C ₁₆ H ₂₀ ClN ₃ O ₅	9.91	9.97	3.92	3.99	201.8–202.6	2.54	2.59	10.16	10.27	
2	C ₆ H ₁₃ ^g	160.1–161.0°	C ₁₆ H ₁₈ ClN ₃ O ₅	9.97	10.02	3.94	3.84	208.0–210.0°	2.55	2.56	10.20	10.11	
2	C ₆ H ₁₃ ^h	151.0–151.5°	C ₁₆ H ₂₀ ClN ₃ O ₅	9.59	9.69	3.79	3.74	196.0–197.5°	2.49	2.54	9.96	9.75	
3	C ₆ H ₁₃ ^g	189.9–190.3	C ₁₆ H ₂₀ ClN ₃ O ₅	9.59	9.44	3.79	3.70	210.0–211.6	2.49	2.55	9.96	9.95	
3	C ₆ H ₁₃ ^h	157.8–158.7	C ₁₇ H ₂₂ ClN ₃ O ₅	9.24	9.20	3.65	3.63	177.2–180.6	2.43	2.46	9.72	9.85	

^a See ref. 14. ^b See ref. 18. ^c With decomposition. ^d Calcd.: C, 45.65; H, 4.47. Found: C, 45.74; H, 4.75. ^e Calcd.: N, 11.02. Found: N, 11.08. ^f Calcd.: C, 48.91; H, 5.28. Found: C, 49.17; H, 5.00. ^g 1-Piperidyl. ^h 2-Methyl-1-piperidyl.

 TABLE II
 2-ALKOXY-4-AMINO- AND 4-NITROBENZONITRILES



X	R	Formula	M.p., °C.	Analyses, %			
				Carbon		Nitrogen	
				Calcd.	Found	Calcd.	Found
NO ₂	C ₆ H ₅	C ₉ H ₅ N ₂ O ₃	151.5–152.4	56.25	56.37	4.20	4.07
NO ₂	C ₆ H ₇	C ₁₀ H ₇ N ₂ O ₃	104.2–105.0	58.24	58.20	4.89	4.92
NO ₂	C ₆ H ₉	C ₁₁ H ₉ N ₂ O ₃	101.8–102.7	59.99	60.25	5.49	5.40
NH ₂ ^a	CH ₃	C ₈ H ₅ N ₂ O	100.1–101.4 ^b	64.85	64.91	5.44	5.30
NH ₂	C ₂ H ₅	C ₉ H ₇ N ₂ O	104.2–105.6	66.64	66.95	6.21	6.02
NH ₂ ^c	C ₆ H ₇	C ₁₀ H ₇ N ₂ O	61.8–62.5	68.15	68.38	6.87	6.58
NH ₂ ^d	C ₆ H ₉	C ₁₁ H ₉ N ₂ O	Oil

^a The hydrochloride had m.p. 195.5–196.2°. Calcd. for C₈H₅ClN₂O: Cl, 19.20. Found: Cl, 19.30. ^b Cook, *et al.*, ref. 17, gives m.p. 102°. ^c The hydrochloride had m.p. 184.7–187.2°. Calcd. for C₁₀H₇ClN₂O: Cl, 16.68. Found: Cl, 16.52. ^d The hydrochloride had m.p. 153.5–156.5°. Calcd. for C₁₁H₉ClN₂O: Cl, 15.64. Found: Cl, 15.41.

ca. 50° (cf. the hydrate obtained by Borsche¹). For the large-scale preparation of this compound it was found more convenient to use the following synthesis: A stirred mixture of 308 g. (2 moles) of 2-hydroxy-4-nitroaniline (m.p. 202.5–204° (dec.)), 364 ml. (4.4 moles) of concentrated hydrochloric acid and 1100 g. of ice was treated during 20 minutes with a solution of 140 g. (2 moles) of sodium nitrite in 400 ml. of water. The internal temperature was maintained at less than 5° by the occasional addition of ice. The resulting bright red-orange suspension of the diazoxide¹⁶ was stirred at 0–5° for 20 minutes, filtered through a cold buchner funnel, and the diazoxide was washed with ice-water (2 × 500 ml.).

The moist, solid diazoxide was added in portions to a vigorously stirred solution of 232 g. of technical cuprous cyanide and 191 g. of technical sodium cyanide in 1200 ml. of water. The internal temperature was maintained at 75–80° during the addition of the diazoxide, and foaming was controlled by the dropwise addition of ether. When addition of the diazoxide was complete (20 minutes) the dark brown mixture was maintained at 75–80° for 30 minutes and then treated with 300 ml. of glacial acetic acid (hood!). The resulting heterogeneous mixture was cooled to 10°, filtered, and the precipitate was washed thoroughly with cold water. After thorough drying at 50° *in vacuo*, the solid was extracted twice, first with 1500 ml. and then with 500 ml. of boiling ethyl acetate. The hot ethyl acetate extracts were decolorized with Darco G 60 and concentrated to dryness *in vacuo*. Recrystallization of the residue from methanol gave 193–223 g. (59–68% yield) of pure 2-hydroxy-4-nitrobenzonitrile, m.p. 162–163°. The mixed melting point with an authentic sample, prepared by the method of Borsche,¹ was 162–163°. The acetyl derivative melted at 97.0–98.6° (lit.¹ m.p. 100°).

2-Methoxy-4-nitrobenzonitrile.—Two methods were used for the preparation of this compound. A modification of

the method of Cook, *et al.*,¹⁷ was used on a large scale. It was found that by conducting the Sandmeyer reaction at 75–80° (foaming controlled by the addition of ether in a thin stream), the yields could be increased to 84–92% of material melting at 174–176°. The pure compound formed cream-colored leaflets from ethyl acetate, m.p. 180.0–180.5°, in agreement with Cook, *et al.*¹⁷

A stirred mixture of 16.4 g. (0.1 mole) of 2-hydroxy-4-nitrobenzonitrile, 18 g. (0.13 mole) of powdered anhydrous potassium carbonate, 22.3 g. (0.12 mole) of methyl *p*-toluenesulfonate (or an equivalent amount of methyl benzenesulfonate) and 400 ml. of *m*-xylene was refluxed under a water trap for 3 hours. The initial deep carmine color of the potassium 2-hydroxy-4-nitrobenzonitrile changed to pale yellow during this period. The mixture was filtered while hot, and the insoluble material was washed thoroughly with hot ethyl acetate. The combined filtrates were concentrated to dryness *in vacuo* and the residual solid was recrystallized from ethyl acetate. There was thus obtained a quantitative yield of 2-methoxy-4-nitrobenzonitrile, m.p. and mixed m.p. 180.0–180.5°.

2-Alkoxy-4-nitrobenzonitriles.—The reaction between 2-hydroxy-4-nitrobenzonitrile, anhydrous potassium carbonate and an alkyl *p*-toluenesulfonate (or benzenesulfonate) in *m*-xylene was carried out as above; using a 7-, 68- and 96-hour reflux and stirring period, respectively, for the ethyl, propyl and butyl compounds (0.1 mole runs) the yields were 95–100%. 2-Ethoxy-4-nitrobenzonitrile was recrystallized from methanol and the propoxy and butoxy homologs were recrystallized from Skellysolve B. These compounds are listed in Table II.

The Forced Reaction of MNBC with Dialkylaminoalkanol.—During the investigation of the reaction mechanism, a number of large scale experiments were carried out. An example follows:

A mixture of 66.6 g. (0.30 mole) of pure, dry MNBC,

(16) G. T. Morgan and J. W. Porter, *J. Chem. Soc.*, **107**, 655 (1915); R. Meldola and J. V. Eyre, *Chem. News*, **83**, 286 (1901).

(17) A. H. Cook, I. M. Heilbron, K. J. Reed and M. N. Strachan, *J. Chem. Soc.*, 861 (1945).

38.7 g. (0.33 mole) of redistilled 2-diethylaminoethanol and 1200 ml. of dry toluene was distilled slowly through a 14" vacuum-jacketed Vigreux column surmounted by a total-reflux variable take-off distillation head. A total of 300 ml. of distillate was collected during 7 hours. The evolved gases were trapped and tested; carbon dioxide was shown to be produced steadily throughout the reaction, but carbon monoxide and unsaturates were absent. During this distillation the still contents darkened to brown. The toluene was removed from the still residue *in vacuo* and the residual yellow-brown solid was treated as follows:

A.—A weighed portion was extracted several times with hot Skellysolve C and the combined Skellysolve C extracts were decolorized and cooled. The crystalline product, after several recrystallizations from absolute alcohol, formed shiny yellow plates, m.p. 104.5–105.5°. The compound was stable toward hot 4% aqueous sodium hydroxide solution (differentiation from MNBC or the basic ester, I) and readily gave a crystalline picrate (m.p. 170.1–170.8°) and hydrochloride (m.p. 193.0–194.0°). A mixed m.p. of the pure base with pure 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile, synthesized for comparison (*vide infra*) showed no depression. Similarly, the mixed melting points of the corresponding picrates and hydrochlorides were undepressed.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, ¹⁴5.32; N, ¹⁸5.32; mol. wt., 263. Found: C, 59.43; H, 6.55; N, ¹⁴5.32; N, ¹⁸5.28; mol. wt. (cryoscopic in dioxane), 271. The weight of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile obtained corresponded to a 67% conversion of the MNBC.

B.—A twenty-gram portion was allowed to stand at room temperature in the open air for 8 days. The solid material slowly sintered to a sticky, bright orange paste. The material was extracted three times with boiling Skellysolve C (from the Skellysolve C extracts was recovered 13.6 g. of pure 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile). The Skellysolve-insoluble material was suspended in warm ethyl acetate and an insoluble red precipitate was removed by filtration (*vide infra*). The ethyl acetate filtrate was decolorized and cooled well in ice. The resulting crystalline precipitate was filtered off and washed thoroughly with a cold 1:1 Skellysolve B-ethyl acetate mixture. Further recrystallization from an ethyl acetate-Skellysolve B mixture gave 4.2 g. of a compound crystallizing in rosettes of brilliant yellow-orange needles, m.p. 146.9–147.4°. A solution of this compound in ethyl acetate, when treated with ethereal hydrogen chloride, gave a crystalline hydrochloride, m.p. 193.2–194.4°, showing no depression of m.p. on admixture with 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile hydrochloride. From the mother liquors from this treatment was isolated a compound melting at 161–162°, showing no m.p. depression on admixture with a sample of pure 2-hydroxy-4-nitrobenzonitrile.

When mixed with a synthetic sample of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile di-(2-cyano-5-nitrophenolate) (*cf.* IV), the above product gave no m.p. depression.

The red ethyl acetate- and Skellysolve C-insoluble precipitate above was recrystallized several times from absolute alcohol-Skellysolve B, forming brilliant red-orange prisms, m.p. 206.3–206.7° (dec.). The material weighed 0.2 g.

Anal. Found: C, 56.38; H, 5.15; N, ¹⁴6.59; N, 16.48.

The compound was recovered unchanged when treated with excess 2-hydroxy-4-nitrobenzonitrile in alcoholic solution. Treatment of this compound with an excess of picric acid in alcoholic solution gave (from the mother liquors) 2-hydroxy-4-nitrobenzonitrile, identified by mixed melting point, and an insoluble picrate, which crystallized from glacial acetic acid in brilliant yellow leaflets, m.p. 268.0–270.0°.

Anal. Found: C, 44.28; H, 4.98; N, 12.71.

The structure of the basic moiety of the red solid is unknown; judging from the melting point of the picrate and from the deep red color of the 2-cyano-5-nitrophenolate this portion is a quaternary compound. These data rule out the structures 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile mono-(2-cyano-5-nitrophenolate) and 2-diethylaminoethanol di-(2-cyano-5-nitrophenolate). The unknown was not identical with 1,1,4,4-tetraethylpiperazinium di-(2-cyano-5-nitrophenolate) (*cf.* III) or with diethyl (2-hydroxyethyl)-

methyllummonium di-(2-cyano-5-nitrophenolate) (*cf.* IX), prepared for comparison (*vide infra*).

C.—A further portion of the original reaction product was powdered and extracted several times with warm 15% aqueous sodium bisulfite solution. From the solution was recovered, by treatment with 35% aqueous sodium hydroxide solution, pure 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile. The insoluble material was dried, extracted several times with boiling ethyl acetate (extracts discarded) and recrystallized from hot water. The product crystallized in white cottony needles, m.p. 220.2–220.6° (dec.). A mixed m.p. with a synthetic specimen of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile bisulfite, XIX, prepared from the base, sodium bisulfite solution and a few drops of acetic acid, showed no depression.

Anal. Calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.54; N, ¹⁸4.06; N, 12.17; S, 9.28. Found: C, 45.58; H, 5.46; N, ¹⁸3.85; N, 12.07; S, 9.48.

3-(2-Methyl-1-piperidyl)-propanol.—A mixture of 44.4 g. (0.20 mole) of MNBC, 39.2 g. (0.25 mole) of redistilled 3-(2-methyl-1-piperidyl)-propanol and 350 ml. of dry toluene was refluxed with slow distillation (*vide supra*) for 6 hours. The toluene was removed from the dark brown still contents *in vacuo*, and the residual brown oil was triturated with several portions of Skellysolve A (the insoluble portion was shown to be MNBC).

A.—A portion of the Skellysolve A solution on evaporation, followed by recrystallization of the residual solid several times from Skellysolve B with decolorization, gave a compound crystallizing in pale yellow leaflets, m.p. 93.1–93.9°. The mixed m.p. with pure 2-(3-(2-methyl-1-piperidyl)-propoxy)-4-nitrobenzonitrile, prepared for comparison (*vide infra*), was undepressed, and the mixed m.p. of the corresponding picrates showed no depression.

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: N, ¹⁴4.62; N, ¹⁸4.62. Found: N, ¹⁴4.72; N, ¹⁸4.63.

B.—A further portion of the Skellysolve A solution was evaporated to dryness and the residual crude solid was allowed to stand in the open air at room temperature for eight days. The spongy resinous orange solid was then extracted several times with hot Skellysolve B (extracts discarded). The insoluble material was dissolved in ethyl acetate and the solution decolorized. A small portion of this solution on treatment with an equal volume of Skellysolve B gave an orange precipitate. The latter, when recrystallized from a small volume of ethyl acetate, formed orange needles melting at 131.6–132.8° and showed no depression of m.p. on admixture with a synthetic sample of 2-(3-(2-methyl-1-piperidyl)-propoxy)-4-nitrobenzonitrile mono-(2-cyano-5-nitrophenolate) (*vide infra*). Further, treatment of this orange solid with ethereal hydrogen chloride yielded pure 2-(3-(2-methyl-1-piperidyl)-propoxy)-4-nitrobenzonitrile hydrochloride and pure 2-hydroxy-4-nitrobenzonitrile, as shown by mixed melting points.

2-(1-Piperidyl)-ethanol.—This reaction was carried out in the manner described for 2-diethylaminoethanol, above. The reaction products were isolated by similar methods. In each case the structures were shown by analyses, by degradation, and by mixed melting points with synthetic samples. There were obtained: 2-(2-(1-piperidyl)-ethoxy)-4-nitrobenzonitrile, in amount corresponding to a 38% conversion of MNBC, and 2-(2-(1-piperidyl)-ethoxy)-4-nitrobenzonitrile di-(2-cyano-5-nitrophenolate), from moisture degradation of the crude reaction product.

2-Dimethylaminoethanol.—A mixture of 44.4 g. (0.20 mole) of MNBC, 22.3 g. (0.25 mole) of redistilled 2-dimethylaminoethanol and 250 ml. of dry toluene was slowly distilled during 5 hours, as above. After cooling the still residue, the toluene layer was decanted from a layer of heavy orange-red oil (*vide infra*).

A.—The toluene layer, after decolorization, was treated with an excess of ethereal hydrogen chloride. The resulting white precipitate was recrystallized from alcohol-ethyl acetate, yielding 32.6 g. of product as white leaflets, m.p. 172.1–173.0°. The mixed m.p. with pure 2-dimethylaminoethyl 6-nitrobenzoxazole-3-carboxylate hydrochloride showed no depression. The combined mother liquors on evaporation gave a small amount of recovered MNBC, but no trace of 2-(2-dimethylaminoethoxy)-4-nitrobenzonitrile could be found.

B.—The toluene-insoluble layer, above, was triturated with cold ethyl acetate, and the resulting insoluble red solid

(18) Basic amino nitrogen determined by titration with perchloric acid in glacial acetic acid solution.

was recrystallized several times from alcohol. There was thus obtained 4.0 g. of brilliant, deep orange needles, m.p. 214.0–214.6°. On drying at 100° *in vacuo* the color of the compound changed to deep carmine; the color faded to orange again when the dried solid was allowed to stand in the air. The orange solid was shown by analysis to be a tetrahydrate of the red solid.

A weighed portion of the red solid was treated, in alcoholic solution, with an excess of ethereal hydrogen chloride (solution faded to colorless) and the resulting clear solution was evaporated to dryness. An ethyl acetate extraction of the residual solid yielded pure 2-hydroxy-4-nitrobenzonitrile, as shown by mixed m.p. The ethyl acetate-insoluble material crystallized from methanol-ether in tiny white prisms, m.p. 340–342°. A mixed m.p. with an authentic sample of 1,1,4,4-tetramethylpiperazinium dichloride¹⁹ showed no depression.

Anal. Calcd. for $C_8H_{10}Cl_2N_2$: C, 44.65; H, 9.37; Cl, 32.95. Found: C, 44.88; H, 9.06; Cl, 32.90.

The weight of each product obtained indicated a ratio of two moles of 2-hydroxy-4-nitrobenzonitrile to one mole of the piperazinium moiety.

A mixed m.p. of the red solid with a synthetic specimen of 1,1,4,4-tetramethylpiperazinium di-(2-cyano-5-nitrophenolate), III, (*vide infra*) gave no depression.

Anal. Calcd. for $C_{22}H_{26}N_6O_8$: C, 56.16; H, 5.57; N, 14.596; N, 18.596. Calcd. for $C_{22}H_{26}N_6O_8 \cdot 4H_2O$: H_2O , 13.28. Found (red crystals): C, 56.40; H, 5.46; N, 14.589; N, 18.604. Found (orange crystals): H_2O , 13.58.

The Rearrangement of Pure Dialkylaminoalkyl 6-Nitrobenzisoxazole-3-carboxylates, I. 2-(1-Piperidyl)-ethyl Ester.—To a solution of 31.5 g. of pure 2-(1-piperidyl)-ethyl 6-nitrobenzisoxazole-3-carboxylate hydrochloride in 400 ml. of cold water was added an excess of solid sodium bicarbonate. The precipitated base was extracted into cold toluene, and the clear pale yellow toluene solution was dried over two successive portions of Drierite, at 10°. Under these conditions no decomposition of the free base was noted. A small aliquot portion of the filtered solution was placed in a crystallizing dish and allowed to evaporate in the air (*vide infra*), and the remainder was refluxed under anhydrous conditions for 24 hours. During this entire period carbon dioxide was slowly but steadily evolved; the solution at the end of the reflux period was dark orange-brown in color, but clear and homogeneous. The toluene was removed *in vacuo* and the residual solid (completely soluble in Skellysolve C, therefore free of structures of type IV or V) was recrystallized from Skellysolve C with decolorization. The pale yellow product was heated with 500 ml. of aqueous 4% sodium hydroxide solution in order to destroy unreacted 2-(1-piperidyl)-ethyl 6-nitrobenzisoxazole-3-carboxylate. From this treatment, after recrystallization of the sodium hydroxide-insoluble material from ethyl acetate-Skellysolve B, was obtained pure 2-(2-(1-piperidyl)-ethoxy)-4-nitrobenzonitrile, m.p. and mixed m.p. 115.0–116.0°. The weight of this product represented a 51.7% conversion of the basic ester, I, to the nitrile, II.

The aliquot portion of the toluene solution which had been removed above was allowed to stand in the air for eight days. During this period the initially yellow crystalline base sintered to an orange sticky paste, then resolidified slowly to a spongy orange solid. From this material were obtained, by methods similar to those described previously: 2-(2-(1-piperidyl)-ethoxy)-4-nitrobenzonitrile, isolated as the picrate, 2-(2-(1-piperidyl)-ethoxy)-4-nitrobenzonitrile di-(2-cyano-5-nitrophenolate) and 2-(1-piperidyl)-ethanol mono-(2-cyano-5-nitrophenolate), (*cf.* V), yellow-orange prisms from ethyl acetate-Skellysolve B, m.p. 85.0–86.3°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: N, 14.478; N, 18.478. Found: N, 14.482; N, 18.468.

3-(1-Piperidyl)-propyl Ester.—The rearrangement of this compound was carried out by exactly the same method used with the 2-(1-piperidyl)-ethyl ester above. The only products of the reaction in boiling dry toluene were carbon dioxide and 2-(3-(1-piperidyl)-propoxy)-4-nitrobenzonitrile (29.5% conversion of the basic ester in 24 hours). From a portion of the pure base which had been allowed to stand in the air for eight days were isolated: 2-(3-(1-piperidyl)-propoxy)-4-nitrobenzonitrile (very small amount), 2-(3-(1-piperidyl)-

propoxy)-4-nitrobenzonitrile mono-(2-cyano-5-nitrophenolate), and 3-(1-piperidyl)-propanol di-(2-cyano-5-nitrophenolate) (*cf.* V), yellow-orange prisms from ethyl acetate-Skellysolve B, m.p. 98.4–100.0°.

Anal. Calcd. for $C_{22}H_{26}N_6O_7$: N, 14.594; N, 18.297. Found: N, 14.600; N, 18.297.

2-Diethylaminoethyl Ester.—The rearrangement of the pure base in dry boiling toluene for 24 hours gave only 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile (71% conversion) and carbon dioxide. When allowed to stand in the air for ten days, the pure base was converted into: 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile, 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile di-(2-cyano-5-nitrophenolate), 2-diethylaminoethanol, isolated as the picrate, and the red-colored unknown of m.p. 206.0–207.0° previously described (trace only).

2-Dimethylaminoethyl Ester.—The pure base was very unstable, rearranging slowly in dry toluene solution even at 10°. When the rearrangement was carried out as above, using a 10-hour reflux period, there was obtained a ca. 70% conversion of the basic ester into carbon dioxide and 1,1,4,4-tetramethylpiperazinium di-(2-cyano-5-nitrophenolate), III. No trace of 2-(2-dimethylaminoethoxy)-4-nitrobenzonitrile could be detected. When allowed to stand in the air, the pure base gave the same decomposition products.

2-(2-Methyl-1-piperidyl)-ethyl Ester.—The pure base, in toluene solution, was refluxed for 24 hours in the presence of a one mole proportion of water. The mixture very rapidly developed an orange color, and carbon dioxide was evolved vigorously. From the reaction mixture, after removal of toluene, were isolated the corresponding homologs of II (22% yield) and IV (10% yield) as well as 2-(2-methyl-1-piperidyl)-ethanol (isolated as the picrate).

The Reaction of MNBC with Amines. Primary Amines.—A mixture of 44.4 g. (0.20 mole) of MNBC, 0.3 mole of a dialkylaminoalkylamine and 300 ml. of toluene was refluxed for from 5 to 9 hours. The toluene was removed *in vacuo* and the residual crystalline product was washed thoroughly with Skellysolve A. The insoluble residue was dissolved in ethyl acetate, the solution was decolorized, and there was added to the filtrate an excess of 20% ethereal hydrogen chloride. The resulting crystalline hydrochloride was recrystallized from alcohol. The yields of pure hydrochlorides varied from 70–85%. The pure hydrochloride was converted to the base by means of aqueous potassium carbonate solution, and the pure base was recrystallized from Skellysolve C. The amides and their derivatives are listed in Table III.

The crystalline bases were very stable; prolonged refluxing in dry toluene solution brought about little or no perceptible decomposition.

The reaction was straightforward even with ethanolamine and 3-diethylamino-2-hydroxypropylamine. In both cases a small amount of darkening of the solution during the reaction was noted, but no trace of material arising from the rearrangement of an ester could be found. Carbon dioxide could not be detected. N-(2-Hydroxyethyl)-6-nitrobenzisoxazole-3-carboxamide crystallized from toluene in rosettes of slender, pale yellow needles, m.p. 153.0–153.7°.

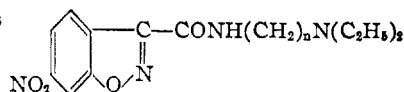
Anal. Calcd. for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.61; N, 14.558. Found: C, 47.61; H, 3.45; N, 14.552.

Secondary Amines.—A solution of 11.1 g. (0.05 mole) of MNBC and 6.8 g. (0.08 mole) of piperidine in 250 ml. of dry toluene was refluxed for 6 hours. The toluene was removed *in vacuo* and the residual solid was recrystallized from methanol. N-(1-Piperidyl)-6-nitrobenzisoxazole-3-carboxamide crystallized in white needles, m.p. 110.0–111.2°.

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.47; H, 4.61; N, 15.35.

Tertiary Amines. Triethylamine.—A solution of 44.4 g. (0.20 mole) of MNBC and 21.2 g. of pure, dry triethylamine in 400 ml. of dry toluene was refluxed for 32 hours. During this entire period carbon dioxide was slowly evolved, but carbon monoxide and unsaturates were absent in the gas. The toluene was removed from the deep brown reaction mixture *in vacuo*, and the residual oil was again evaporated *in vacuo* with fresh toluene to ensure removal of the excess triethylamine. The residual oil was extracted several times with hot Skellysolve C (from these extracts was recovered 19.4 g. of pure MNBC). The Skellysolve C-insoluble material was recrystallized several times from small amounts of absolute alcohol, yielding 8.8 g. of pure 2-methoxy-4-nitro-

(19) *cf.* G. A. C. Gough and H. King, *J. Chem. Soc.*, 2437 (1928); O. Eisleb, *Ber.*, 74, 1433 (1941).

TABLE III
 N-(DIETHYLAMINOALKYL)-6-NITROBENZISOXAZOLE-3-CARBOXAMIDES


n	Formula	M.p., °C.	Base		M.p., °C.	Hydrochloride				M.p., °C.	Picrate			
			Analyses, % Nitrogen ^a			Analyses, % Nitrogen ^b		Analyses, % Chlorine			Analyses, % Nitrogen ^a		Analyses, % Nitrogen ^b	
			Calcd.	Found		Calcd.	Found	Calcd.	Found		Calcd.	Found	Calcd.	Found
2	C ₂₁ H ₂₈ N ₄ O ₆ ^c	61.0–63.0	4.57	4.58	227.0–228.5	4.09	4.32	10.34	10.44	174.2–175.2	2.62	2.59	10.48	10.14
3	C ₂₃ H ₃₀ N ₄ O ₆ ^d	89.0–89.5	4.37	4.36	232.5–233.5 ^e	15.70 ^f	15.44 ^f	9.94	9.90	161.4–163.4	2.55	2.52	10.20	9.95
4	C ₂₅ H ₃₂ N ₄ O ₆ ^g	59.0–60.0	4.19	4.14	173.0–174.8 ^h	3.78	3.64	9.56	9.50	127.4–128.2	2.49	2.49	9.96	9.50
i	C ₂₇ H ₃₄ N ₄ O ₆ ^j	119.8–120.7	4.16	4.18	209.0–209.7	3.76	3.98	9.51	9.66	205.8–206.6	2.48	2.50	9.92	9.75

^a See ref. 18. ^b See ref. 14. ^c Calcd.: N, 14.457. Found: N, 14.460. ^d Calcd.: C, 56.24; H, 6.29. Found: C, 56.35; H, 5.89. ^e With decomposition. ^f Total nitrogen by Dumas. ^g Calcd.: C, 57.47; H, 6.63. Found: C, 57.54; H, 6.58. ^h The hydrochloride formed a monohydrate of the same melting point. Anal. Calcd. for C₂₅H₃₂ClN₄O₆·H₂O: C, 49.42; H, 6.48; N, 14.360; H₂O, 4.63. Found: C, 49.75; H, 6.48; N, 14.348; H₂O, 4.42. ⁱ 3-Diethylamino-2-hydroxypropyl. ^j Calcd.: N, 14.416. Found: N, 14.420.

benzonitrile, m.p. and mixed m.p. with an authentic sample, 179.2–181.0°.

Anal. Calcd. for C₂₁H₂₈N₄O₆: N, 14.786. Found: N, 14.789.

The combined alcoholic mother liquors were treated with a large volume of Skellysolve A and the precipitated heavy red oil was separated by decantation. The red oil (melting point ca. 15°) was dissolved in ethyl acetate, the solution was treated with an excess of solid 2-hydroxy-4-nitrobenzonitrile (color change from red to orange), and Skellysolve B was added to crystallization. The product formed large, golden-yellow feathery leaflets from ethyl acetate-Skellysolve B, m.p. 129.7–130.6°. The compound showed no depression of m.p. on admixture with a synthetic sample of methyltriethylammonium di-(2-cyano-5-nitrophenolate) (cf. VIII), prepared for comparison.

Anal. Calcd. for C₂₁H₂₈N₆O₆: N, 14.632; N, 18, 3.16; N, 15.79. Found: N, 14, 5.98; N, 18, 3.17; N, 15.70.

A solution of the compound in absolute alcohol was treated with an absolute alcoholic solution of picric acid, added dropwise until the color of the solution changed from orange to yellow. The precipitate was filtered off and recrystallized from absolute alcohol. The product formed long, slender, golden-yellow needles, m.p. 276.5–277.4°. Lossen²⁰ reported a melting point of 267–268° for methyltriethylammonium picrate.

Anal. Calcd. for C₁₈H₂₀N₄O₇: C, 45.35; H, 5.85; N, 14.1220; N, 18, 4.07. Found: C, 45.53; H, 5.79; N, 14.1235; N, 18, 4.10.

When the above reaction was carried out with only a catalytic amount of triethylamine, the evolution of carbon dioxide was very slow and only a trace of methyltriethylammonium di-(2-cyano-5-nitrophenolate) was obtained. No 2-methoxy-4-nitrobenzonitrile could be found in the reaction products.

1-Methylpiperidine.—The substitution of 1-methylpiperidine for triethylamine in the above reaction gave analogous results. A reaction carried out with equivalent amounts of the components (refluxing for 28 hours) gave 11.6 g. of pure 2-methoxy-4-nitrobenzonitrile, 8.4 g. of recovered MNBC and a red oil, soluble in absolute alcohol and in ethyl acetate but insoluble in Skellysolve B. On treatment in ethyl acetate solution with excess 2-hydroxy-4-nitrobenzonitrile (color change of the solution from red to orange), the latter oil was converted to 1,1-dimethylpiperidinium di-(2-cyano-5-nitrophenolate) (cf. VIII), orange prisms from ethyl acetate-Skellysolve B, m.p. 165.8–166.5°.

Anal. Calcd. for C₂₁H₂₈N₆O₆: N, 14.635; N, 18, 3.18. Found: N, 14.635; N, 18, 3.21.

The red oil was shown to be 1,1-dimethylpiperidinium mono-(2-cyano-5-nitrophenolate) by the semi-quantitative isolation of 2-hydroxy-4-nitrobenzonitrile and of 1,1-dimethylpiperidinium iodide, m.p. 335–336° (dec.) (lit.²¹ m.p. 334° (dec.)). Further, both salts on treatment with picric acid solution gave 1,1-dimethylpiperidinium picrate as long, slender, canary-yellow needles from dilute alcohol, m.p. 308–310° (dec.).

Anal. Calcd. for C₁₈H₂₀N₄O₇: N, 18, 4.09; N, 14, 12.27. Found: N, 18, 4.11; N, 14, 12.11.

(20) W. Lossen, *Ann.*, **181**, 374 (1876).

(21) E. Wedekind and R. Oechsle, *Ber.*, **35**, 1076 (1902).

Ethyl 6-Nitrobenzisoxazole-3-carboxylate and 1-Methylpiperidine.—A solution of 23.6 g. (0.10 mole) of ethyl 6-nitrobenzisoxazole-3-carboxylate and 12.0 g. (0.12 mole) of pure 1-methylpiperidine in 350 ml. of dry *m*-xylene was refluxed for 28 hours. Carbon dioxide was very slowly evolved throughout the reflux period. The mixture was then cooled, the supernatant xylene layer was carefully decanted from the small amount of heavy black oil, and the oil was rinsed with a small amount of xylene.

The xylene solution was decolorized and evaporated to dryness *in vacuo*. The residual solid was repeatedly warmed with portions of 4% aqueous sodium hydroxide solution in order to destroy unreacted ethyl 6-nitrobenzisoxazole-3-carboxylate. The insoluble material on recrystallization from methanol formed pale yellow leaflets, m.p. 150–151°. The mixed melting point of this compound with a known sample of 2-ethoxy-4-nitrobenzonitrile was not depressed. The yield was ca. 500 mg.

The xylene-insoluble heavy oil (above) was divided into two portions. One portion, on treatment with 2-hydroxy-4-nitrobenzonitrile in ethyl acetate solution gave 1-methyl-1-ethylpiperidinium di-(2-cyano-5-nitrophenolate), long, slender golden-yellow needles from ethyl acetate-Skellysolve B, m.p. 138.4–138.8°.

Anal. Calcd. for C₂₂H₂₈N₆O₆: N, 14.616. Found: N, 14.646.

The second portion gave, when treated with picric acid solution 1-methyl-1-ethylpiperidinium picrate, golden-yellow needles from absolute alcohol, m.p. 271.7–272.3°.

Anal. Calcd. for C₁₄H₂₀N₄O₇: N, 18, 3.93; N, 14, 11.79. Found: N, 18, 3.98; N, 14, 11.88.

When a mixture of *n*-hexyl 6-nitrobenzisoxazole-3-carboxylate and triethylamine was refluxed in toluene for 48 hours only traces of carbon dioxide were evolved and no material corresponding to 2-*n*-hexyloxy-4-nitrobenzonitrile could be isolated.

The Reaction of Methyl Benzoylformate with Triethylamine.—A mixture of 16.4 g. (0.10 mole) of methyl benzoylformate, 11.0 g. (0.11 mole) of pure, dry triethylamine and 250 ml. of dry toluene was refluxed for 24 hours. No gases were evolved during this period. The mixture was cooled and the toluene layer was decanted from the heavy semi-crystalline paste. From this paste (ca. 6.7 g.) was isolated, by treatment with picric acid solution, pure methyltriethylammonium picrate, m.p. and mixed m.p. 276–277°. By treatment with concentrated hydrochloric acid and extraction, crystalline benzoylformic acid was also isolated.

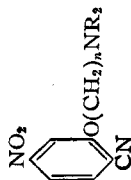
The Reaction of Methyl Benzoylformate with Potassium-2-hydroxy-4-nitrobenzonitrile.—A suspension of potassium 2-hydroxy-4-nitrobenzonitrile in xylene was mixed with a slight excess of methyl benzoylformate, and the mixture was refluxed with stirring for 16 hours. The color of the red potassium salt was unaltered; on working up the reaction mixture no trace of 2-methoxy-4-nitrobenzonitrile could be detected.

The Synthesis of 2-(Dialkylaminoalkoxy)-4-nitrobenzonitriles.—A number of synthetic methods for the preparation of the 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles were investigated. These are listed below. The compounds prepared, as well as characterizing derivatives, are listed in Table IV.

Method A.—To a warm solution of 82.0 g. (0.50 mole) of 2-hydroxy-4-nitrobenzonitrile in 1000 ml. of absolute alcohol

TABLE IV

2-DIALKYLAMINOALKOXY-4-NITROBENZONITRILES



#	R ₁	M.p., °C.	Formula	Base Analyses, %			Hydrochloride Analyses, %			Picrate Analyses, %			Methiodide Analyses, %		
				Nitrogen ^a	Calcd.	Found	Nitrogen ^b	Calcd.	Found	Nitrogen ^b	Calcd.	Found	Nitrogen ^b	Calcd.	Found
2	(CH ₃) ₂	83.1-84.0	C ₁₂ H ₁₄ N ₄ O ₄	5.95	5.98	5.95	13.05	12.79	5.16	5.28	189.5-191.0	3.02	3.04	12.08	11.79
2	(C ₂ H ₅) ₂	104.5-105.5	C ₁₄ H ₁₈ N ₄ O ₄	5.32 ^d	5.28	5.32	11.83	11.75	14.02 ^e	14.02 ^e	170.2-171.0	2.84	2.84	11.36	11.45
2	(C ₂ H ₅) ₂	53.6-55.0	C ₁₄ H ₁₈ N ₄ O ₄	5.05	5.04	5.05	11.30	11.30	4.46	4.58	168.8-169.8	2.77	2.78	11.08	10.98
2	C ₆ H ₁₃ ^f	118.1-119.2	C ₁₈ H ₂₂ N ₄ O ₄	5.09	5.07	5.09	11.37	11.33	4.49	4.64	191.6-192.8	2.78	2.80	11.12	10.88
2	C ₆ H ₁₃ ^f	133.4-136.2	C ₁₈ H ₂₂ N ₄ O ₄	4.84 ^g	4.82	4.82	10.88	10.80	12.90 ^g	13.04 ^g	214.3-215.6 ^g	2.70	2.71	10.80	10.89
2	C ₆ H ₁₃ ^f	132.9-133.8	C ₁₈ H ₂₂ N ₄ O ₄	4.62	4.65	4.62	10.43	10.30	4.12	4.26	223.0-225 ^g	2.63	2.69	10.52	10.50
3	C ₆ H ₁₃ ^f	102.2-102.8	C ₁₈ H ₂₂ N ₄ O ₄	4.84	4.87	4.84	10.88	10.83	4.30	4.30	175.0-175.8	2.70	2.73	10.80	10.85
3	C ₆ H ₁₃ ^f	92.5-93.5	C ₁₈ H ₂₂ N ₄ O ₄	4.62	4.64	4.62	10.43	10.27	12.37 ^g	12.12 ^g	153.7-155.1	2.63	2.65	10.52	10.45
2	C ₆ H ₁₃ ^h	126.5-127.5	C ₁₈ H ₂₂ N ₄ O ₄	5.05	5.07	5.05	11.30	11.31	4.47	4.35	185.5-186.6	2.77	2.77	11.08	11.19
3	C ₆ H ₁₃ ^h	110.0-111.5	C ₁₈ H ₂₂ N ₄ O ₄	4.81	4.82	4.81	10.82	10.85	4.27	4.19	189.5-190.4	2.69	2.73	10.76	10.80

^a See ref. 18. ^b See ref. 14. ^c Crystallized as a semi-hydrate. Prolonged drying at 110° *in vacuo* was necessary in order to render anhydrous. ^d Calcd.: C, 59.43; H, 6.51. Found: C, 59.43; H, 6.58. ^e Total nitrogen by the Dumas method. ^f Calcd.: C, 41.49; H, 4.97. Found: C, 41.46; H, 4.78. ^g With decomposition. ^h 1-Piperidyl. ⁱ Sintered at 197°, slowly decomposed and turned black above 199°. ^j 2-Methyl-1-piperidyl. ^k Calcd.: C, 62.26; H, 6.62. Found: C, 62.38; H, 6.53. ^l 2,6-Dimethyl-1-piperidyl. ^m 4-Morpholinyl.

was added a solution of 11.5 g. (0.50 mole) of sodium in 500 ml. of absolute alcohol. To the resulting deep carmine-colored solution was added 74.5 g. (0.55 mole) of 2-diethylaminoethyl chloride,²² the mixture was refluxed with stirring for 5 hours, filtered while hot, and the filter-cake was washed thoroughly with absolute alcohol. The combined filtrates were evaporated *in vacuo*, the residue was dissolved in ethyl acetate, and the solution was filtered. To the filtrate was added an excess of 20% ethereal hydrogen chloride solution. The resulting precipitate of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile hydrochloride was filtered off and recrystallized several times from absolute alcohol-ether. The yield of pure material was 112.0 g. (85%).

The pure hydrochloride was dissolved in water and the base was precipitated by means of solid potassium carbonate. 2-(2-Diethylaminoethoxy)-4-nitrobenzonitrile crystallized from Skellysolve C in large, pale yellow leaflets. The conversion yield was 97%.

When a 3-dialkylaminopropyl chloride was substituted in the above procedure, there was added 6 g. of sodium iodide per mole of chloride base and the reflux period was increased to 20 hours. The yields of pure 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles varied from 65 to 90%.

The substitution of 2-dimethylaminoethyl chloride in the above reaction gave none of the desired product. Instead, cyclization of the 2-dimethylaminoethyl chloride occurred exclusively, and a high yield of 1,1,4,4-tetramethylpiperazinium di-(2-cyano-5-nitrophenolate), III, was isolated. The m.p. and mixed m.p. with a synthetic sample (*vide infra*) was 212.4-213.3° (dec.).

1-Dimethylamino-2-chloropropane gave a mixture of products indicating that partial cyclization of the basic chloride had occurred.

The alcoholic filtrate from the reaction (carried out as above) was evaporated *in vacuo*. The residual red oil was triturated with warm ethyl acetate and the insoluble red precipitate (*vide infra*) was removed by filtration. The ethyl acetate solution was decolorized and treated with an excess of ethereal hydrogen chloride. The resulting crystalline hydrochloride was filtered off, washed with ethyl acetate, and reconverted to the base; the crystalline base as initially obtained melted at 56-59°. Several recrystallizations from Skellysolve C and from dilute alcohol gave cream-colored leaflets, m.p. 75.6-77.0°. This compound has either structure XVII or XVIII.

Anal. Calcd. for C₁₂H₁₄N₄O₄: N, 14 5.62; N, 18 5.62. Found: N, 14 5.60; N, 18 5.58.

The hydrochloride formed pale yellow prisms from alcohol, m.p. 212.1-212.7°.

Anal. Calcd. for C₁₂H₁₄ClN₄O₄: N, 14 4.90; Cl, 12.41. Found: N, 14 5.04; Cl, 12.39.

The picrate crystallized from dilute alcohol in long, slender, canary-yellow needles, m.p. 174.0-175.8°.

Anal. Calcd. for C₁₈H₁₈N₆O₁₀: N, 18 2.93; N, 14 11.72. Found: N, 18 2.94; N, 14 11.92.

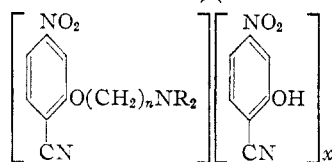
The ethyl acetate-insoluble red precipitate, above, was recrystallized several times from absolute alcohol-Skellysolve B or from "wet" isopropyl alcohol. The compound crystallized in clusters of slender red needles from the former solvents and in large thin rectangular orange plates from the latter solvent. The orange form (a hydrate) was converted to the red form on drying at 100°. Both forms had m.p. 168.4-169.0°. Quantitative degradation experiments conducted by the method previously outlined, indicated that this compound was 1,1,2,4,4,5-hexamethylpiperazinium di-(2-cyano-5-nitrophenolate), XVI.

Anal. Calcd. for C₂₄H₃₀N₆O₆: C, 57.82; H, 6.07; N, 14 5.62; N, 18 5.62. Found: C, 57.49; H, 6.08; N, 14 5.84; N, 18 5.72.

From the degradation experiments were isolated 1,1,2,4,4,5-hexamethylpiperazinium dipicrate, small canary-yellow needles from dilute alcohol, m.p. 286.0° (dec.) (*Anal.* Calcd. for C₂₂H₂₈N₆O₁₄: N, 14 13.37; N, 18 4.46. Found: N, 14 13.09; N, 18 4.55); and 1,1,2,4,4,5-hexamethylpiperazinium dichloride, hygroscopic white needles from isopropyl alcohol-ethyl acetate, m.p. 261.6° (dec.).

Anal. Calcd. for C₁₀H₁₄Cl₂N₂: Cl, 29.16. Found: Cl, 28.95.

(22) The distilled free base may be conveniently replaced by the equivalent amount of the pure hydrochloride and an additional equivalent of sodium ethoxide.

TABLE V
 (2-(DIALKYLAMINOALKOXY)-4-NITROBENZONITRILE)-(2-HYDROXY-4-NITROBENZONITRILE) SALTS


n	R ₂	x	Formula	M.p., °C.	Analyses, %			
					Nitrogen ^a		Nitrogen ^b	
					Calcd.	Found	Calcd.	Found
2	(CH ₃) ₂	2	C ₂₆ H ₂₁ N ₇ O ₉	148.0-148.9	2.49	2.52	7.46	7.55
2	(C ₂ H ₅) ₂	2	C ₂₇ H ₂₅ N ₇ O ₉ ^c	147.2-147.9	2.37	2.36	7.10	6.88
3	(C ₂ H ₅) ₂	2	C ₂₈ H ₂₇ N ₇ O ₉	117.0-118.5	2.31	2.32	6.94	6.85
2	C ₆ H ₁₀ ^d	2	C ₂₈ H ₂₅ N ₇ O ₉	157.0-158.0	2.32	2.34	6.96	6.80
2	C ₆ H ₁₂ ^e	1	C ₂₂ H ₂₃ N ₅ O ₆	169.4-170.0	3.09	3.06	6.17	6.18
2	C ₇ H ₁₄ ^f	1	C ₂₃ H ₂₅ N ₅ O ₆	175.5-178.0	2.99	2.99	5.99	5.96
3	C ₆ H ₁₀ ^d	1	C ₂₂ H ₂₃ N ₅ O ₆	144.3-145.5	3.09	3.08	6.17	6.16
3	C ₆ H ₁₂ ^e	1	C ₂₃ H ₂₅ N ₅ O ₆	132.4-133.0	3.00	3.01	5.99	5.91
2	C ₄ H ₈ O ^g	1	C ₂₀ H ₁₉ N ₅ O ₇	151.6-153.0	3.17	3.16	6.35	6.15
3	C ₄ H ₈ O ^g	1	C ₂₁ H ₂₁ N ₅ O ₇	136.0-138.0	3.07	3.07	6.15	6.22

^a See ref. 18. ^b See ref. 14. ^c Calcd.: C, 54.82; H, 4.26. Found: C, 54.83; H, 4.26. ^d 1-Piperidyl. ^e 2-Methyl-1-piperidyl. ^f 2,6-Dimethyl-1-piperidyl. ^g 4-Morpholinyl.

Method B.—A stirred mixture of 82.0 g. (0.50 mole) of 2-hydroxy-4-nitrobenzonitrile, 70.3 g. (0.52 mole) of powdered anhydrous potassium carbonate and 2500 ml. of toluene was refluxed under a water trap for 3 hours. During this period 4.5 ml. of water was collected. The trap was removed and there was added 54.0 g. (0.50 mole) of 2-dimethylaminoethyl chloride. The stirred mixture was refluxed for 16 hours, treated an additional 10.8 g. (0.10 mole) of 2-dimethylaminoethyl chloride, and refluxed for an additional 8 hours. The mixture was filtered while hot, the insoluble material was washed with hot toluene, and the combined filtrates were decolorized and evaporated *in vacuo*. The resulting solid was recrystallized several times from Skellysolve C, yielding 77.1 g. (65.7%) of pure 2-(2-dimethylaminoethoxy)-4-nitrobenzonitrile.

Method C.—The reaction between 2-hydroxy-4-nitrobenzonitrile, anhydrous potassium carbonate and 2-chloroethyl *p*-toluenesulfonate, in xylene solution, was carried out by the procedure used in the synthesis of the 2-alkoxy-4-nitrobenzonitriles above. A reflux period of 78 hours was used. From the filtered, evaporated xylene solution was obtained a 67.5% yield of pure 2-(2-chloroethoxy)-4-nitrobenzonitrile, slender, pale yellow needles from absolute alcohol, m.p. 127.4-128.5°.

Anal. Calcd. for C₉H₇ClN₂O₃: N, 14.618; Cl, 15.65. Found: N, 14.630; Cl, 15.30.

The reaction of this intermediate with a secondary amine in aqueous-alcoholic solution containing sodium iodide, in the usual manner, gave fair to poor yields of the 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles.

Method D.—A solution of 16.4 g. (0.10 mole) of 2-hydroxy-4-nitrobenzonitrile and 14.2 g. (0.11 mole) of 2-diethylaminoethyl chloride in 150 ml. of anhydrous isopropyl alcohol was refluxed for 5 hours. On working up there was obtained 8.5 g. (28% yield) of 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile hydrochloride, m.p. and mixed m.p. 193-194°.

Method E.—A solution of 6.2 g. (0.03 mole) of 6-nitrobenzisoxazole-3-carboxylic acid¹ and 5.4 g. (0.04 mole) of 2-diethylaminoethyl chloride in 100 ml. of anhydrous isopropyl alcohol was refluxed for one hour. During initial solution of the acid in the alcohol-amine mixture an orange color developed and carbon dioxide was vigorously evolved. On working up there was obtained 5.2 g. (58% yield) of pure 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile hydrochloride, m.p. and mixed m.p. 193.2-194.6°.

Anal. Calcd. for C₁₃H₁₈ClN₂O₃: C, 52.09; H, 6.05; N, 14.02; Cl, 11.83. Found: C, 52.29; H, 5.91; N, 14.07; Cl, 11.79.

The Synthesis of 2-Cyano-5-nitrophenolates. 2-(Dialkylaminoalkoxy)-4-nitrobenzonitrile Salts, IV.—A mixture of 0.01 mole of the pure 2-(dialkylaminoalkoxy)-4-nitrobenzonitrile and 0.02 mole of pure 2-hydroxy-4-nitrobenzonitrile

(both accurately weighed) was dissolved in 100 ml. of boiling ethyl acetate. On cooling the product usually crystallized; if necessary Skellysolve B was added to incipient turbidity. The salt was then recrystallized from ethyl acetate or ethyl acetate-Skellysolve B to constant melting point and spectral purity. These salts are listed in Table V. The 1:1 salts were an orange to scarlet color and the 1:2 salts were yellow to orange-yellow. The salt with 2-(2-(2-methyl-1-piperidyl)-ethoxy)-4-nitrobenzonitrile was dimorphic, the low melting metastable form melting at 152.0-153.0°. On seeding a melt of the low melting form, held at 154°, with the high melting form, resolidification ensued and remelting occurred at 169.0-169.8°. The salt of XVII or XVIII crystallized in a mixture of golden-yellow needles and scarlet needles, corresponding in all probability to the 1:2 and 1:1 forms, respectively.²³ These salts could not be separated by recrystallization, and even a mechanical separation did not give a spectrally pure salt.

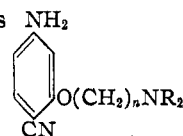
Triethylamine Salt.—An equimolecular mixture of pure triethylamine and pure 2-hydroxy-4-nitrobenzonitrile gave only triethylammonium di-(2-cyano-5-nitrophenolate), yellow prisms from ethyl acetate-Skellysolve B, m.p. 89.3-90.8°.

Anal. Calcd. for C₂₀H₂₃N₅O₆: N, 14.652; N, 18.326. Found: N, 14.677; N, 18.327.

Methyltriethylammonium Di-(2-cyano-5-nitrophenolate) (cf. VIII).—To a solution of 16.4 g. (0.10 mole) of 2-hydroxy-4-nitrobenzonitrile and 4.0 g. (0.10 mole) of sodium hydroxide in 200 ml. of warm water was added a solution of 17.0 g. (0.10 mole) of silver nitrate in 50 ml. of water. The resulting slurry of silver 2-cyano-5-nitrophenolate was mixed thoroughly, and the precipitate was filtered off and washed well with water and with alcohol. The moist silver salt was added to 0.10 mole of methyltriethylammonium iodide (prepared *in situ* from 10.1 g. of triethylamine and 15.6 g. of methyl iodide) in 60 ml. of alcohol, and the resulting stirred suspension was refluxed for one hour. The silver iodide was filtered off and washed with absolute alcohol. The combined filtrates were evaporated *in vacuo*; the residual methyltriethylammonium mono-(2-cyano-5-nitrophenolate) was a viscous scarlet oil, m.p. ca. 0°. To a weighed portion of the oil in hot ethyl acetate solution was added an equimolecular amount of pure 2-hydroxy-4-nitrobenzonitrile; the color of the solution lightened from scarlet to yellow-orange. The mixture was diluted while hot with an equal volume of Skellysolve B and cooled. The resulting crystalline precipitate formed large, brilliant, orange plates from ethyl acetate-Skellysolve B, m.p. 129.0-130.8°.

Anal. Calcd. for C₂₁H₂₅N₅O₆: C, 56.87; H, 5.68; N, 14.632. Found: C, 56.94; H, 5.65; N, 14.643.

(23) Since a sharp-melting base was used in this preparation, it seems unlikely that these two crystalline forms represent derivatives of XVII and XVIII present in admixture.

TABLE VI
 4-AMINO-2-(DIALKYLAMINOALKOXY)-BENZONITRILES


n	R ₂	Base	M.p., °C.	Formula	Analyses, % Nitrogen		M.p., °C.	Phosphate Analyses, %				M.p., °C.	Flavinate Analyses, % Sulfur	
					Calcd.	Found		Calcd.	Found	Calcd.	Found		Calcd.	Found
2	(C ₂ H ₅) ₂	Oil		C ₁₅ H ₁₉ N ₃ O	213.5–214.5	29.59	29.70	12.68	12.52	144.6–145.5 ^a	6.06 ^b	5.98 ^b
3	(C ₂ H ₅) ₂	96.0–96.6		C ₁₄ H ₁₇ N ₃ O	17.00	16.91	237.5–238.2	28.39	28.52	12.17	11.92	194.5–196.0	5.71	5.70
2	C ₄ H ₉ ^c	Oil		C ₁₄ H ₁₉ N ₃ O	198.0–198.7	28.55	28.60	12.24	12.05	225.8–226.3 ^d	5.73	5.81
2	C ₆ H ₁₃ ^e	Oil		C ₁₆ H ₂₁ N ₃ O	192.5–194.0	27.43	27.50	11.76	11.56	211.0–212.0	5.59	5.36
2	C ₇ H ₁₅ ^f	96.2–96.8		C ₁₅ H ₂₁ N ₃ O	10.25 ^b	10.02 ^b	193.5–195.5	26.40	26.10	11.31	11.19	219.3–220.7	5.46	5.51
3	C ₈ H ₁₇ ^c	125.6–126.9		C ₁₆ H ₂₁ N ₃ O	16.20	16.28	202.1–203.3	27.43	27.83	11.76	11.60	224.0–225.7	5.59	5.61
3	C ₈ H ₁₇ ^e	111.8–113.4		C ₁₅ H ₂₁ N ₃ O	10.25 ^b	9.97 ^b	214.8–216.7	26.40	26.40	11.31	11.20	227.7–228.5 ^d	5.46	5.45
2	C ₄ H ₉ O ^g	130.6–132.8		C ₁₅ H ₁₇ N ₃ O ₂	17.00	17.09	222.2–223.5 ^h	12.49 ⁱ	12.21 ⁱ	14.81	14.77	241.4–242.0	5.71	5.77
3	C ₄ H ₉ O ^g	90.4–91.4		C ₁₄ H ₁₉ N ₃ O ₂	16.08	15.96	190.5–192.2	27.28	27.52	11.69	11.55	222.8–224.7	5.57	5.61

^a Monopicate. ^b See ref. 18. ^c 1-Piperidyl. ^d With decomposition. ^e 2-Methyl-1-piperidyl. ^f 2,6-Dimethyl-1-piperidyl. ^g 4-Morpholinyl. ^h Monohydrochloride. ⁱ Chlorine analysis.

One-tenth mole portions of the mono- and the di-salts were separately mixed with 250 ml. of dry toluene and the heterogeneous mixtures were refluxed for 36 hours. On working up each reaction only the starting material was recovered; no trace of 2-methoxy-4-nitrobenzonitrile could be detected in either reaction.

Tetraalkylpiperazinium Salts.—The piperazinium salts were readily prepared, in nearly quantitative yields, from two moles of silver 2-cyano-5-nitrophenolate and one mole of the tetraalkylpiperazinium dichloride, by the above procedure.

1,1,4,4-Tetramethylpiperazinium di-(2-cyano-5-nitrophenolate), III, scarlet needles (anhydrous—*vide supra*), m.p. 212.0–213.0°.

Anal. Calcd. for C₂₂H₂₆N₆O₆: C, 56.16; H, 5.57; N, 18.596. Found: C, 56.27; H, 5.28; N, 18.6.00.

1,1,4,4-Tetraethylpiperazinium di-(2-cyano-5-nitrophenolate), brilliant orange-red prisms from alcohol, m.p. 192.8–193.2° (dec.).

Anal. Calcd. for C₂₆H₃₄N₆O₆: C, 59.30; H, 6.51; N, 18.532. Found: C, 59.20; H, 6.49; N, 18.532.

1,1,4,4-Bis-pentamethylenepiperazinium di-(2-cyano-5-nitrophenolate),²⁴ scarlet prisms from alcohol, m.p. 201.6–202.4°.

Anal. Calcd. for C₂₈H₃₄N₆O₆: C, 61.07; H, 6.22; N, 18.509. Found: C, 61.04; H, 6.21; N, 18.520.

Diethyl (2-Hydroxyethyl)-methylammonium Di-(2-cyano-5-nitrophenolate) (cf. IX).—The reaction of silver 2-cyano-5-nitrophenolate with diethylaminoethanol methiodide²⁵ and the isolation of the product as the disalt was carried out as above. The compound crystallized from ethyl acetate-Skellysolve B in blunt red-orange needles, m.p. 90.2–95.5°.

Anal. Calcd. for C₂₁H₂₆N₆O₇: N, 15.24; N, 18.3.05. Found: N, 14.99; N, 18.3.09.

A solution of the compound in absolute alcohol readily yielded **diethyl-(2-hydroxyethyl)-methylammonium picrate**, canary-yellow needles from absolute alcohol, m.p. 239.9–240.5°.

Anal. Calcd. for C₁₉H₂₁N₄O₈: N, 18.3.88; N, 14.11.64. Found: N, 18.3.90; N, 14.11.70.

2-Alkoxy-4-aminobenzonitriles.—The 2-alkoxy-4-nitrobenzonitriles were reduced by hydrogenation (50 p.s.i., 25°) in absolute alcohol solution, using platinum oxide as catalyst. The reductions were exothermic and very rapid. Recrystallization of the products was best effected from benzene. The compounds prepared in this manner are listed in Table II.

4-Amino-2-(dialkylaminoalkoxy)-benzonitriles.—The 2-(dialkylaminoalkoxy)-4-nitrobenzonitriles were reduced by the general iron-hydrochloric acid procedure previously

outlined.²⁶ A number of the bases thus obtained were crystalline; these were readily recrystallized from Skellysolve C or from dilute alcohol. The yields of pure bases varied from 85 to 95%. The compounds and their derivatives are listed in Table VI.

4-Alkylamino-2-(dialkylaminoalkoxy)-benzonitriles.—The pure 4-amino-2-(dialkylaminoalkoxy)-benzonitriles were reductively alkylated by means of an aliphatic aldehyde, using zinc and acetic acid in benzene solution.²⁶ The bases were viscous, high boiling, pale yellow oils.

4-Butylamino-2-(2-diethylaminoethoxy)-benzonitrile hydrochloride, white cottony needles from absolute alcohol-ethyl acetate, m.p. 210.2–211.0°.

Anal. Calcd. for C₁₇H₂₈ClN₃O: C, 62.67; H, 8.36; N, 12.90; Cl, 10.90. Found: C, 62.72; H, 8.47; N, 12.95; Cl, 10.76.

4-Butylamino-2-(2-(2-methyl-1-piperidyl)-ethoxy)-benzonitrile phosphate, white prisms from alcohol, m.p. 194.4–195.3°.

Anal. Calcd. for C₁₉H₂₈N₃O₅P: N, 10.16; H₃PO₄, 23.17. Found: N, 10.11; H₃PO₄, 23.28.

4-Amylamino-2-(2-(2-methyl-1-piperidyl)-ethoxy)-benzonitrile phosphate, white prisms from alcohol-isopropyl alcohol, m.p. 178.0–179.5°.

Anal. Calcd. for C₂₀H₃₄N₃O₅P: N, 9.83; H₃PO₄, 22.93. Found: N, 9.90; H₃PO₄, 22.58.

4-Amino-2-(dialkylaminoalkoxy)-benzonitrile Methiodides.—The 2-(dialkylaminoalkoxy)-4-nitrobenzonitrile methiodides (cf. Table IV) were catalytically reduced in 80% alcohol solution at 50 p.s.i. and 25°, using platinum oxide as catalyst. The reductions were very rapid, and hydrogen uptake ceased abruptly when three moles had been absorbed. The resulting white product was recrystallized from absolute alcohol or an absolute alcohol-ethyl acetate mixture.

4-Amino-2-(2-diethylaminoethoxy)-benzonitrile methiodide, prisms, m.p. 132.5–134.5°.

Anal. Calcd. for C₁₄H₂₂IN₃O: N, 11.20; I, 33.82. Found: N, 11.50; I, 33.47.

4-Amino-2-(3-diethylaminopropoxy)-benzonitrile methiodide, needles, m.p. 146.4–147.7°.

Anal. Calcd. for C₁₅H₂₄IN₃O: N, 10.80; I, 32.60. Found: N, 10.90; I, 32.44.

4-Amino-2-(3-(1-piperidyl)-propoxy)-benzonitrile methiodide, needles, m.p. 162.9–164.2°.

Anal. Calcd. for C₁₆H₂₄IN₃O: C, 47.88; H, 6.03; I, 31.63. Found: C, 47.73; H, 6.13; I, 31.44.

4-Amino-2-(2-(1-piperidyl)-ethoxy)-benzonitrile methiodide, rosettes of prisms, m.p. 162.0–163.0°.

Anal. Calcd. for C₁₅H₂₂IN₃O: I, 32.77. Found: I, 32.64.

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RECEIVED OCTOBER 8, 1951

(24) For the piperazinium dichloride see W. Marckwald and O. Frobenius, *Ber.*, **34**, 3557 (1901).

(25) B. Emmert, *ibid.*, **45**, 433 (1912).

(26) R. O. Clinton, S. C. Laskowski, U. J. Salvador and M. Wilson, *This Journal*, **73**, 3674 (1951).