Nitrile Oxides. V. Stable Aromatic Nitrile Oxides[1,2]

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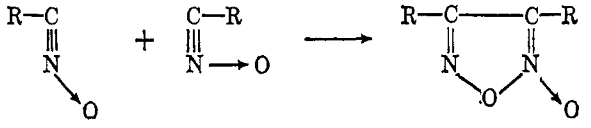
The dehydrogenation of aromatic aldoximes bearing substituents of proper size in the *o,o'* positions by means of alkali hypohalite, preferably hypobromite, leads to aromatic nitrile oxides which are prevented by steric hindrance from the usual fast spontaneous dimerization to furoxans. On prolonged heating these nitrile oxides rearrange neatly to isocyanates. Despite their inability to dimerize, they display all the other known addition reactions of nitrile oxides.

Nitrile oxides are among the most reactive species in organic chemistry. For a long time, however, their instability has seriously impaired their study and is probably the reason that the vast majority of known reactions of nitrile oxides have been studied only with the first discovered member of this series, benzonitrile oxide. All known nitrile oxides dimerize spontaneously to 1,2,5-oxadiazole 1-oxides (furoxans, I).[3] While at ordinary temperature the rate of this reaction is immeasurably fast with simple aliphatic nitrile oxides, aromatic nitrile oxides are completely dimerized within hours or at most days after their preparation.[4]

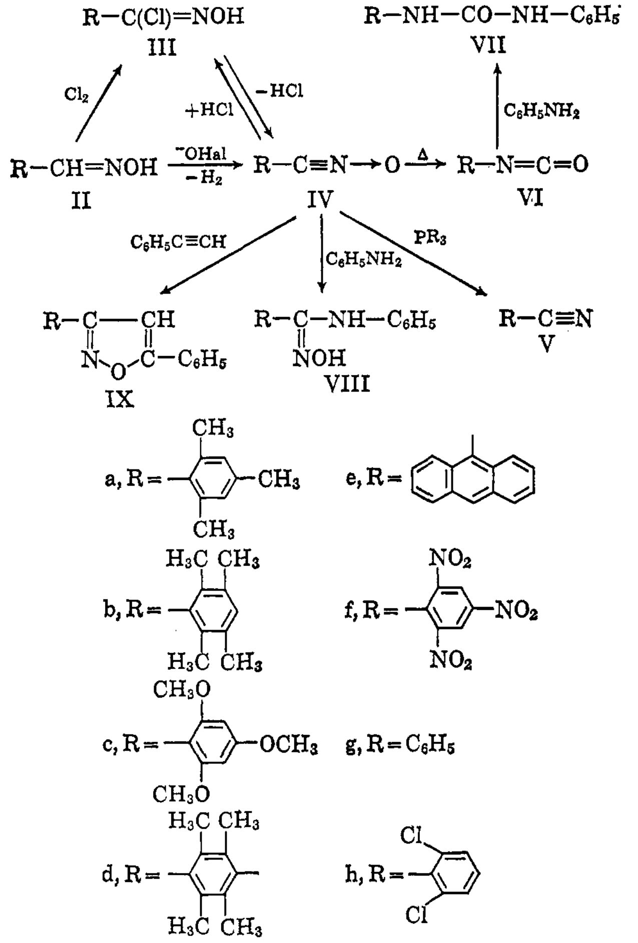


I

Studies of Stuart–Briegleb molecule models indicate that the dimerization reaction should be sterically blocked by bulky substituents in the residue attached to the nitrile oxide group. To test this assumption we chose first aromatic nitrile oxides bearing substituents of proper size at the *o,o'* positions. The models indicate that suitable groups are CH_3, C_2H_5, CH_3O, or CH_3S, while Br, I, NO_2, or SO_2R are probably too large and F, Cl, or OH too small for this purpose.[5]

Thus, the preparation of 2,4,6-trimethylbenzonitrile oxide (IVa) was attempted. The usual synthetic route to nitrile oxides starts with the corresponding aldoxime (II) which is chlorinated to the hydroxamic acid chloride (III) (see Scheme I). By mild treatment with bases, III is converted to the nitrile oxide (IV). It was found, however, that 2,4,6-trimethylbenzaldoxime (IIa) and other methyl-substituted aromatic aldoximes, like IIb, could not be chlorinated to III by any of the known chlorination procedures without a considerable additional uptake of chlorine by the molecule, presumably by substitution in the aromatic ring. Thus, the dehydrochlorination of the crude III invariably yielded mixtures of the desired nitrile oxide with chlorinated products from which analytically pure specimens could be obtained only in minute yields after tedious purification procedures.[6]

Scheme I



It was then found that aromatic aldoximes generally can be dehydrogenated to the nitrile oxides (IV) with good to excellent yields as their oximate anions by means of alkali hypobromite. Thus, a shorter route to IV is now available which avoids the complications involved in the preparation of the hydroxamic acid chlorides. The reaction of aromatic aldoximes with hypochlorite had been studied a long time ago. Among other products, dimeric compounds were obtained which were derived from aldoximes by removal of only one hydrogen atom per molecule and designated in the

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[1] Part IV: C. Grundmann, V. Mini, J. M. Dean, and H.-D. Frommeld, *Ann.*, in press.

[2] Preliminary communication: C. Grundmann and J. M. Dean, *Angew. Chem.*, **76**, 682 (1964); *Angew. Chem. Intern. Ed. Engl.*, **3**, 585 (1964).

[3] For the mechanism, *cf.* R. Huisgen, *Angew. Chem.*, **75**, 751 (1963).

[4] For relative rates of this reaction, *cf.* A. Quilico in "Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., New York, N. Y., 1962, p. 21.

[5] 2,6-Dichlorobenzonitrile oxide is described to dimerize completely to the furoxan within 30–35 days at 18°; G. Speroni, unpublished; *cf.* ref. 4.

[6] S. Califano, R. Moccia, R. Scarpati, and G. Speroni [*J. Chem. Phys.*, **26**, 1777 (1957)] have reported the infrared spectra of IVa and IVb and mentioned briefly that these compounds are more stable than benzonitrile oxide, but without any further details as to their preparation or properties. This was announced to be the subject of a separate communication which has not appeared so far, probably because of the above-mentioned difficulties in obtaining pure compounds by the conventional synthesis *via* the hydroxamic acid chlorides.

TABLE I

STABLE AROMATIC NITRILE OXIDES

Compd.	Oxidizing agent or preferred method[a]	Temp., °C.	Time, hr.	Yield,[b] %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % Mol. wt.	Found, % C	Found, % H	Found, % N	Found, % Mol. wt.[c]
IVa	NaOCl	0	0.75	35	110–112	$C_{10}H_{11}NO$	74.50	6.88	8.69	161	74.21	6.92	8.79	161
	NaOI	0	5	44	111									
	A	5	1	82	114									
IVb	A	10	1	79	118	$C_{11}H_{13}NO$	75.41	7.48	8.00	175	75.30	7.59	8.12	180
IVc	B	0	2	78	160–170[d]	$C_{10}H_{11}NO_4$	57.41	5.30	6.70	209	57.21	5.32	6.59	219
IVd	B	0	2	42	169–170[d]	$C_{12}H_{12}N_2O_2$	66.66	5.60	12.96	216	66.48	5.70	12.80	230
IVe	A,B	3	0.5	58	129[e]	$C_{15}H_9NO$	82.18	4.12	6.39	219	82.39	3.51	6.17	219
IVh	A	−2	2	50[f]	80[g]	$C_7H_3Cl_2NO$	44.72	1.61	7.45	188	44.31	1.67	7.27	197

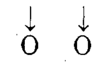
[a] A and B refer to hypobromite oxidation procedures described in the Experimental section. [b] Analytically pure material, usually after one recrystallization; for yields of crude nitrile oxides see ref. 2. [c] Osmometric, in acetone. [d] With decomposition. [e] Although anthracenyl-9-nitrile oxide is stable toward dimerization, it is slowly decomposed upon exposure to air and daylight, as other 9-substituted anthracenes; *cf.* ref. 23. [f] Crude material: 97%; a considerable amount is lost in separating IVh from the minor amounts of furoxan already formed. [g] Lit.[4,5] m.p. 86–87°.

TABLE II

REACTION PRODUCTS FROM STABLE AROMATIC NITRILE OXIDES

Compd.	Yield,[a] %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
			Hydroxamic Acid Chlorides (III)						
IIIa	76	72	$C_{10}H_{12}ClNO$[b]	. . .	. . .	7.09	. . .	. . .	7.46
IIIb	73	124–126[c]	$C_{11}H_{14}ClNO$[d]	. . .	. . .	6.51	. . .	. . .	6.62
IIIc	85	108–111[c]	$C_{10}H_{12}ClNO_4$	48.89	4.92	5.70	49.08	5.05	5.81
IIId	83	158–160[c]	$C_{12}H_{14}Cl_2N_2O_2$	49.84	4.89	9.69	50.02	4.82	9.55
			Arylphenylureas (VII)						
VIIa	68	245	$C_{16}H_{18}N_2O$	75.56	7.14	11.02	75.32	7.24	11.21
VIIb	51[e]	306[f]	$C_{17}H_{20}N_2O$	76.08	7.51	10.44	75.87	7.54	10.17
VIIc	58	227	$C_{16}H_{18}N_2O_4$	63.58	6.00	9.27	63.43	6.19	9.33
VIId	79	*f, g*	$C_{24}H_{26}N_4O_2$	71.62	6.51	13.92	71.59	6.63	13.63
			Aroylanilide Oximes (VIII)						
VIIIa	76	146[c]	$C_{16}H_{18}N_2O$	75.56	7.14	11.02	75.36	7.08	10.89
VIIIb	85	247[c]	$C_{17}H_{20}N_2O$	. . .	. . .	10.44	. . .	. . .	9.97
VIIIc	59	199[c]	$C_{16}H_{18}N_2O_4$	63.58	6.00	9.27	63.72	6.00	9.04
VIIId	72	*f, h*	$C_{24}H_{26}N_4O_2$	71.62	6.51	13.92	71.41	6.75	13.65
			3-Aryl-5-phenylisoxazoles (IX)						
IXa	80	94	$C_{18}H_{17}NO$	82.10	6.51	5.32	81.78	6.56	5.43
IXb	73	175	$C_{19}H_{19}NO$	82.27	6.91	5.05	82.09	6.76	4.74
IXc	83	98	$C_{18}H_{17}NO_4$	69.44	5.50	4.50	69.40	5.65	4.38
IXd	70	312[f]	$C_{28}H_{24}N_2O_2$	79.97	5.75	6.66	79.89	5.81	6.90
IXe	85	149	$C_{23}H_{15}NO$	85.94	4.70	4.36	85.84	4.69	4.31

[a] Analytically pure material, usually after one recrystallization; for yields of crude product see ref. 2. [b] *Anal.* Calcd.: Cl, 17.34. Found: Cl, 17.64. [c] With decomposition. [d] *Anal.* Calcd.: Cl, 16.75. Found: Cl, 16.65. [e] Since moisture was not excluded during the rearrangement reaction of IVb to VIb, an additional 25% of bisdurylurea, m.p. 339°, was obtained. *Anal.* Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.64. Found: C, 77.60; H, 8.46; N, 8.77. [f] Berl-Block. [g] Carbonizes at >360° without melting. [h] Carbonizes at >300° without melting.

literature as "aldoxime peroxides."[7] Recently, they have been recognized as aldazine bis-N-oxides (X),  $\mathrm{Ar{-}CH{=}\underset{\substack{\downarrow\\ O}}{N}{-}\underset{\substack{\downarrow\\ O}}{N}{=}CH{-}Ar}$.[8] Under our reaction conditions, IIa and sodium hypochlorite give a mixture of IVa with the corresponding X,[9] while hypobromite in all cases led quite specifically to the exclusive formation of nitrile oxides. Alkali hypoiodite offers no preparative advantage since the reaction is slower and the yields are much inferior.

The preparation of **2,4,6-trimethylbenzonitrile oxide (IVa)**, **2,3,5,6-tetramethylbenzonitrile oxide (IVb)**, **2,4,6-trimethoxybenzonitrile oxide (IVc)**, **tetramethylterephthalobisnitrile oxide (IVd)**, and **anthracene-9-nitrile oxide (IVe)** by the above method has fully confirmed our anticipations. All these compounds are well-crystallized solids, indefinitely stable at ordinary temperature. Their identity has been established by molecular weight determinations, infrared spectra (all compounds have a strong narrow band around 2300 cm.$^{-1}$, characteristic for aromatic nitrile oxides[10]), and by the reactions discussed below. Experimental data of the prepared nitrile oxides are summarized in Table I.

Our method is likewise applicable to the preparation of nonhindered (unstable) aromatic nitrile oxides, as demonstrated by the conversion of 2,6-dichlorobenzaldoxime (IIh) to **2,6-dichlorobenzonitrile oxide (IVh)**.[5,9] Attempts, to dehydrogenate 2,4,6-trinitrobenzaldoxime

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[7] G. Ponzio and G. Busti, *Gazz. chim. ital.*, **36**, 339 (1906); R. Ciusa and E. Parigi, *ibid.*, **53**, 142 (1923).

[8] L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.*, **61**, 290 (1961).

[9] We thank Dr. H.-D. Frommeld for performing this experiment.

[10] R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **26**, 546 (1960); S. Califano, R. Moccia, R. Scarpati, and G. Speroni, *J. Chem. Phys.*, **26**, 1777 (1957); S. Califano, R. Scarpati, and G. Speroni, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis., mat. nat.*, **23**, 263 (1958).

(IIf) to IVf failed, since the nitro groups in the *ortho* and *para* positions apparently take part in the formation of the anion of IIf in a way known for analogous polynitro compounds.[11] The resulting species is very sensitive and the oxime IIf cannot be recovered from an alkaline solution. The conventional route to the nitrile oxide is likewise blocked; IIf fails to react with chlorine, probably because of excessive steric hindrance as predicted by the models.

Trimethyl phosphite reduces the nitrile oxides IVa–e almost quantitatively to the corresponding nitriles (Va–e).[12]

Attempts to force the dimerization to furoxans by heating the nitrile oxides IVa–e above their melting point or by refluxing them in a high-boiling solvent, such as xylene or decalin, have resulted in a clean rearrangement to the corresponding isocyanates (VI) with no furoxan formation. Previously, this rearrangement has been observed only as minor side reaction on heating a solution of benzonitrile oxide (IVg) in xylene to reflux while the majority of IVg is converted to diphenylfuroxan (I, R = C_6H_5).[13] The isocyanates VIa–d were identified as the substituted phenylureas VIIa–d by reaction with aniline; VIe was converted by ethanol to the ethyl anthracenyl-9-carbamate.

In spite of their lack of reactivity in dimerization, these sterically hindered nitrile oxides still display the characteristic addition reactions of the nitrile oxide group.[14] Hydrogen chloride forms the **hydroxamic chlorides (III)**, aniline leads to the formation of the **phenylamidoximes (VIII)**, and phenylacetylene, in a typical 1,3-dipolar cycloaddition, gives the **3-aryl-5-phenylisoxazoles (IX)**. A number of the derivatives thus obtained are compiled in Table II.

So far the study of the reactions of nitrile oxides has been confined to those which occur at a comparable or faster rate than the dimerization to furoxans. The sterically hindered stable nitrile oxides offer opportunities to investigate reactions which do not meet the above requirement. A number of novel nucleophilic addition reactions have already been discovered and will be reported in a subsequent paper, as well as a mechanistic study of the rearrangement of nitrile oxides to isocyanates.

Experimental[15]

Starting Materials.—2,4,6-Trimethylbenzaldoxime (IIa) was prepared according to literature[16] from the commercially available aldehyde. The obtained IIa is a mixture of the *syn* and *anti* forms (m.p. 124 and 181°). It was used after one recrystallization from aqueous methanol, m.p. 124–127°, since control experiments with the pure stereoisomers did not reveal any significant difference in the dehydrogenation procedure. 2,3,5,6-Tetramethylbenzaldoxime (IIb), m.p. 137°, was prepared in 90% yield from the crude aldehyde obtained from bromodurene *via* the Grignard reaction with ethyl orthoformate.[17] 2,4,6-Trimethoxybenzaldoxime (IIc) and the alkali-soluble β-anthracene 9-aldoxime (IIe) were prepared as described in the literature.[18] For the synthesis of tetramethylterephthaldialdehyde we followed the directions of the patent literature[19]; the crude aldehyde, however, proved to be a mixture of the desired dialdehyde and 4-hydroxymethyl-2,3,5,6-tetramethylbenzaldehyde. A 7.1-g. sample of this mixture, m.p. 156–165°, was dissolved in a heated mixture of methanol (75 ml.) and water (25 ml.), filtered from insoluble impurities, and cooled to room temperature, whereby tetramethylterephthaldialdehyde (3.0 g.) separated in long thin needles, m.p. 164–165°. This material proved satisfactory for the preparation of the dioxime.

Tetramethylterephthaldialdoxime (IId).—To a hot solution of tetramethylterephthaldialdehyde (3.0 g.) in methanol (50 ml.) there was added in one portion a warm solution of 3.0 g. of hydroxylamine hydrochloride and 6.0 g. of crystalline sodium acetate in 15 ml. of water. The initially clear mixture was heated for several minutes on the steam bath while a thick crystalline precipitate formed. After addition of 35 ml. of water, the reaction mixture was cooled to +5°, filtered, and washed thoroughly with water. The crude oxime (3.06 g., 88%) was further purified by one recrystallization from acetic acid, m.p. 234–238°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 65.46; H, 7.33; N, 12.72. Found: C, 65.27; H, 7.38; N, 12.62.

This product is obviously a mixture of stereoisomers, but no further attempt was made to separate them, since fractions with melting points varying between 227 and 256° behaved identically in the nitrile oxide synthesis. Any material, however, softening below 225° still contains 4-hydroxymethyl-2,3,5,6-tetramethylbenzaldoxime.

The methanolic mother liquor of the tetramethylterephthaldialdehyde yielded on oximation by the same procedure an oxime much more soluble in methanol, which was purified by repeated recrystallizations from methanol–water (2:1) and xylene resulting finally in small needles, m.p. 182–183°, of **4-hydroxymethyl-2,3,5,6-tetramethylbenzaldoxime.**

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.77. Found: C, 69.66; H, 8.11; N, 6.43.

Dehydrogenation of Aldoximes to Nitrile Oxides. Procedure A.—The aldoxime (50 mmoles) was dissolved, if necessary with slight warming, in 2 *N* NaOH (100 ml.). The solution was cooled by an ice–water bath, disregarding the occasional crystallization of part of the sodium salt of the oxime, and with efficient stirring 80 ml. of a solution of bromine in carbon tetrachloride (1 ml. = 0.1 g. of Br) was added dropwise over a period of 1 hr. while the temperature was maintained at +1°. After the addition of the bromine, the reaction mixture was stirred for 1 hr. more at 25°, the organic layer was separated, and the aqueous phase was extracted with ether (50 ml.). The organic solvents were combined, dried over anhydrous sodium sulfate, and evaporated at the water pump at a maximum bath temperature of 40°. The crude nitrile oxides remaining were recrystallized from methanol or ligroin. This method works well with nitrile oxides which are sufficiently soluble in CCl_4; otherwise emulsions which are difficult to separate may result. Also, in cases where the aldoxime is very sensitive to halogen, such as IIc, procedure B is to be preferred.

Procedure B.—The aldoxime (20 mmoles) was dissolved in 40 ml. of 1 *N* NaOH. The sodium salts of 2,4,6-trimethoxybenzaldoxime and β-anthracene 9-aldoxime were found to be very little soluble in water, but by addition of 10–15 ml. of pyridine complete solution was achieved. The clear solution was added dropwise over a period of 1 hr. with vigorous stirring to a previously prepared solution of 3.35 g. (calcd. 3.20 g.) of bromine in 100 ml. of ice-cold 1 *N* NaOH.[20] By means of an ice

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(11) *Cf.* J. Meisenheimer, *Ann.*, **323**, 205 (1902).

(12) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **30**, 2077 (1965).

(13) H. Wieland, *Ber.*, **42**, 4207 (1909).

(14) H. Wieland [*Ber.*, **40**, 1669 (1907)] claims that benzonitrile oxide (IVg) does not react with hydrogen chloride or aniline. We have convinced ourselves that this statement is erroneous; IVg adds these reagents as easily as the nitrile oxides described in this paper with the formation of the corresponding derivatives IIIg and VIIIg.

(15) If not indicated otherwise, all melting points were determined with the Fisher-Johns melting point apparatus; microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(16) A. Hantzsch and A. Lucas, *Ber.*, **28**, 747 (1895); R. Scholl and F. Kačer, *ibid.*, **36**, 330 (1903).

(17) L. I. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941); modified according to Houben-Weyl, "Methoden der Organischen Chemie," Vol. VII, 4th Ed., Georg Thieme Verlag, Stuttgart, 1954, p. 65, footnote 4, Georg Thieme, Stuttgart, 1954.

(18) J. Herzig and H. Gehringer, *Monatsh.*, **23**, 868 (1903); J. Kenyon and R. F. Mason, *J. Chem. Soc.*, 4964 (1952); L. F. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.*, **60**, 2555 (1938); J. S. Meek and J. R. Dann, *ibid.*, **77**, 6677 (1955).

(19) L. A. Mikeksa and D. F. Koennecke (to Esso Research and Engineering Co.), U. S. Patent 2,806,883 (1957); *Chem. Abstr.*, **52**, 5470*g* (1958).

(20) With tetramethylterephthaldialdoxime the amounts of alkali and bromine have to be doubled, since there are two aldoxime functions to be oxidized.

bath the temperature was maintained during this period at 0°. After addition of the oxime solution stirring was continued at 0° for 30 min. more, and the finely divided precipitate was filtered as quickly as possible through a large Büchner funnel. The precipitate was washed several times with ice-water, then dried thoroughly over KOH *in vacuo*. In the case of tetramethylterephthalobisnitrile oxide (IVd) the crude product consisted to a considerable part of an apparently higher molecular material, from which IVd could be easily extracted with methylene chloride. IVd was then recrystallized from methylene chloride–methanol. Also, the crude anthracene-9-nitrile oxide (IVe) contained some higher molecular impurities. Pure IVe was best obtained by extraction of the crude material with small portions of boiling ligroin (b.p. 60–70°) until no more IVe crystallized out on chilling the extracts in ice.

The nature of these higher molecular by-products is not yet clear. It is certain, however, that they are not the corresponding furoxans; preliminary investigations indicate that they result from a 1,3-dipolar addition of the nitrile oxide to the oximate anion.

Rearrangement of Nitrile Oxides to Isocyanates.—The nitrile oxide (2 mmoles) was refluxed for 5 hr. in dry xylene (20 ml.). To the hot xylene solution, there was added aniline (4.2 mmoles), whereupon the mixed phenylarylureas crystallized out on cooling. A second fraction was obtained on concentration of the mother liquor *in vacuo*. The mixed ureas VIIa–c were recrystallized from aqueous acetic acid. The urea VIId obtained from tetramethylterephthalobisnitrile oxide precipitated already analytically pure; it was extremely difficultly soluble in all common organic solvents, but could be recrystallized from quinoline–ethanol. The nitrile oxides IVa and IVb could also be rearranged by heating without a solvent to 120–125° for 8 hr.; this method, however, failed with the other nitrile oxides. From the melt of IVa, there was isolated 2,4,6-trimethylphenyl isocyanate (VIa), m.p. 45°, and identified with a specimen prepared by known routes.[21] 1-Phenyl-3-(2′,4′,6′-trimethylphenyl)-urea (VIIa) was also identified by mixture melting point with an authentic sample.[22] The anthracenyl-9-nitrile oxide was converted into **ethyl anthracenyl-9-carbamate** by dissolving the crude VIe, remaining after evaporation of the xylene *in vacuo*, in an excess of absolute ethanol: yellow small glistening needles, m.p. 233°, lit.[23] m.p. 236.5–237°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.73; H, 5.88; N, 5.36.

Hydroxamic Acid Chlorides (III).—The nitrile oxide (1 mmole) was dissolved in methylene chloride (10 ml.) and ether (5 ml.), and dry hydrogen chloride was passed into the ice-cooled solution until its odor was definitely perceptible. The solvent was then evaporated *in vacuo* and the residue, usually corresponding to the theoretical amount, recrystallized from benzene–petroleum ether.

Aroylanilide Oximes (VIII).—The nitrile oxide (2 mmoles) was dissolved in benzene (30 ml.), a 100% excess of the required amount of aniline was added, and the mixture was heated for 15 min. on the steam bath. The crude amidoxime remaining after evaporation of the solvent *in vacuo* was dissolved in 2 *N* HCl, if necessary filtered from acid-insoluble by-products, and reprecipitated by neutralization with 2 *N* sodium carbonate solution. The anilide oximes were finally purified by recrystallization from aqueous ethanol, with the exception of VIIId, which is quite insoluble in all common organic solvents. The material remaining after successive extraction of the crude product with boiling ethanol and benzene proved to be analytically pure VIIId.

3-Aryl-5-phenylisoxazoles (IX).—The addition of the nitrile oxide (1 mmole) and phenylacetylene (1.1 mmoles) proceeded smoothly on refluxing in benzene (15 ml.) for 15 min. After evaporation of the solvent and excess phenylacetylene, finally at 50° (0.1 mm.), the remaining IX was recrystallized from methanol (IXa–c), acetic acid (IXe), or N-dimethylformamide (IXd).

Acknowledgment.—The research of which this publication forms a part was supported by Public Health Service Research Grant CA 07272-01 and -02 of the National Cancer Institute, Bethesda, Maryland.

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(21) R. Dahlbom and L. E. Österberg, *Acta Chem. Scand.*, **9**, 1563 (1955).

(22) P. Grammaticos, *Bull. soc. chim. France*, 761 (1949).

(23) H. J. Creech and W. R. Franks, *J. Am. Chem. Soc.*, **60**, 127 (1938).

A New Type of 1,4-Benzothiazepine Derivatives

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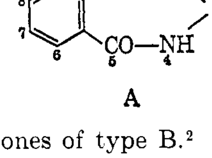
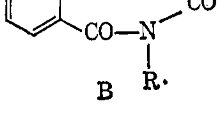
The synthesis of 5-substituted 2,3-dihydro-1,4-benzothiazepines, a hitherto unknown class of heterocyclic compounds, was investigated. Representative compounds were prepared from the appropriate amino ketones I *via* the corresponding mercapto ketones IV. A number of transformations, characteristic for these compounds, are described.

Our interest in the chemistry of 1,4-benzodiazepines led us to investigate other related ring systems. One of these is the little explored group of 1,4-benzothiazepines. Only a few members belonging to this group are known in the literature. These are a tetrahydro-1,4-benzothiazepin-5-one[1] (A) and a few 3,5-diones of type B.[2] Compounds bearing a substituent other than oxygen in position 5 were not yet described.



A



B

In view of the remarkable pharmacological properties of 5-substituted 1,4-benzodiazepines, we were particularly interested in 2,3-dihydro-1,4-benzothiazepines bearing an alkyl, aryl, or pyridyl substituent in position 5. These compounds were conveniently accessible from *o*-mercapto ketones IV[3] which, when condensed with 2-bromoethylamine, usually yielded a mixture of the desired 2,3-dihydro-1,4-benzothiazepine V with its precursor VI. Complete ring closure was achieved by refluxing the mixture (V + VI) in pyridine.

By an alternate route, condensation of 2-chloro-5-trifluoromethylbenzophenone[4] with 2-mercaptoethylamine yielded VIc which could be cyclized in boiling pyridine to the 2,3-dihydro-1,4-benzothiazepine Vc.

The *o*-mercapto ketones IV were obtained by diazotization of the corresponding *o*-amino ketones I, followed by a Sandmeyer-type reaction using either potassium ethyl xanthate or copper thiocyanate, and

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(1) F. Jacob and P. Schlack, *Ber.*, **96**, 88 (1963).

(2) E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 81 (1948).

(3) For compounds I–VIII, see Scheme I.

(4) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).