Chlorination of 1-Chloromercuri-2-nitropropane.—Passage of chlorine gas through a slurry of 1-chloromercuri-2-nitropropane in chloroform for 2 hr led to evolution of some NO_2 fumes and precipitation of 57% of the mercury as its dichloride. From the chloroform were recovered 21% of starting material and 10 ml of a yellow, lachrymatory liquid which contained at least 12 components as indicated by gas chromatographic analyses. None of these corresponded to the expected 1-chloro-2-nitropropane. They were not identified.

Other Reactions of 1-Chloro-2-nitropropane (II).—Triethyl phosphite in refluxing dioxane gave triethyl phosphate, nitric oxide in small amounts, and propylene. No other indentifiable products were found. Acetyl chloride[29] in excess, refluxed for 11 hr, gave no nitro ketone. Although dilute hydrochloric acid decomposes β-nitromercurials immediately to the corresponding olefins, 25% nitric acid may be warmed to about 90° with 1-chloro-2-nitropropane before rapid evolution of oxides of nitrogen occurs. The product contained no identifiable nitro aliphatic compound. Both dilute and concentrated solutions of sodium hydroxide decompose β-nitromercurials rapidly with deposition of metallic mercury, evolution of olefin, and formation in small amounts of gummy organic solids. Steam distillation of the solid yielded no organic product.

Many attempts were made to reduce β-nitromercurials to nitro alkanes, but without any success. Agents tried included a copper–zinc couple in water, sodium borohydride, diborane, platinum oxide and hydrogen, Raney nickel in alcohol, stannous chloride dihyrate in ethyl acetate, and mercury–mercurous chloride in chloroform.

Registry No.—I, 10562-31-9; II, 10562-32-0; III, 10562-33-1; IV, 10562-34-2; V, 10562-35-3; 1-bromomercuri-2-nitrocyclohexane, 10562-36-4; methyl 2-chloromercuri-3-nitropropionate, 10562-37-5; 2-nitro-2-methyl-3-chloromercuri-4-pentanone, 10562-38-6; *cis*-1-bromo-2-nitrocyclohexane, 10562-39-7; *trans*-1-bromo-2-nitrocyclohexane, 10562-40-0.

(29) H. Gilman and G. F. Wright [*J. Am. Chem. Soc.*, **55**, 3302 (1933)] have shown that furan organomercurials can readily be converted to the corresponding furan methyl ketones by the action of acetyl chloride.

Nitrile Oxides. IX. Basic, Substituted, Stable Nitrile Oxides[1]

CHRISTOPH GRUNDMANN AND REINHARD RICHTER

Mellon Institute, Pittsburgh, Pennsylvania 15213

Received January 27, 1967

Nitrile oxides of the benzene and pyrimidine series, stabilized by controlled steric hindrance and substituted by a dimethylamino group, are described, and some of their reactions are discussed. These compounds are the first isolated nitrile oxides which contain an additional different functional group.

The wide variety of organic structures which react spontaneously with nitrile oxides[2] considerably restricts the chances of obtaining nitrile oxides with functional groups. Aside from some difunctional nitrile oxides,[2b] no compounds containing another true functional group have been isolated so far.[3] Since a common procedure for the preparation of nitrile oxides consists in the dehydrohalogenation of hydroxamyl chlorides by triethylamine,[4] it can be

$$RC(NOH)Cl + NEt_3 \longrightarrow RC{\equiv}N{\rightarrow}O + HCl{\cdot}Et_3N$$

assumed that the tertiary amino group is compatible with the CNO group. There are, however, occasional observations that some hydroxamyl chlorides form rather stable quaternary salts with tertiary amines, especially pyridine.[3,5-7] The nitrile oxides described in this paper were protected from spontaneous dimerization to a furoxan (1,2,5-oxadiazole 2-oxide) by controlled steric hindrance, as previously described.[8]

The recently obtained[9] 4-dimethylamino-2,6-dimethylbenzaldehyde (I) and 4-dimethylamino-2,6-dimethylisophthaldialdehyde (II) were converted into the corresponding aldoximes and subjected to alkali hypobromite. Contrary to our experience with simple aromatic nitrile oxides, the dehydrogenation procedure worked satisfactorily only under the very specific conditions given in the Experimental Section. The oxime of I (III) was obtained in the two stereoisomeric forms (*syn* and *anti*). The structural assignment was based on the fact that by reaction with alkali or acetic anhydride, the lower melting isomer was transformed into the corresponding nitrile (VI) and was, therefore, the *anti* oxime, while the higher melting (*syn*) oxime remained unchanged, or yielded an acetate. Only the *syn* oxime reacted readily with alkaline hypobromite to yield 4-dimethylamino-2,6-dimethylbenzonitrile oxide (IV), while the *anti* isomer was converted in poor yield into 4-dimethylamino-3-bromo-2,6-dimethylbenzaldoxime (V).[10] From the outset of our studies of the hypohalogenite oxidation of aldoximes to nitrile oxides,[8] we had anticipated such steric effects, but in the case of the mesitylaldoximes, where both isomers are well known, we have failed to recognize such differences in reactivity, probably because in the alkaline environment the unfavorable (*anti*) configuration is converted rapidly into the favorable (*syn*) configuration. Apparently, it depends entirely on the rate of such alkali-induced isomerization whether steric effects will be observed. Contrary to other aromatic al-

(1) Paper VIII: C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **31**, 4235 (1966).

(2) (a) C. Grundmann and H.-D. Frommeld, *ibid.*, **31**, 157 (1966); (b) C. Grundmann, *Fortsch. Chem. Forsch.*, **7**, 62 (1966), a review of the pertinent literature to 1965.

(3) R. H. Wiley and B. J. Wakefield [*J. Org. Chem.*, **25**, 546 (1960)] prepared 3,5-dichloro-2-hydroxy-benzonitrile oxide in carbon tetrachloride solution and identified the nitrile oxide by its infrared spectrum, but isolated only the corresponding furoxane.

(4) For a review, see C. Grundmann in Houben-Weyl, "Methoden der Organischen Chemie," Vol. X/3, 4th ed, E. Müller, Ed., Georg Thieme, Stuttgart, 1965, pp 841–870.

(5) H. Wieland and A. Höchtlen, *Ann.*, **505**, 237 (1933).

(6) A. Quilico, G. Gaudiano, and A. Ricca, *Gazz. Chim. Ital.*, **87**, 638 (1957).

(7) C. Grundmann, V. Mini, J. M. Dean, and H.-D. Frommeld, *Ann.*, **687**, 191 (1965).

(8) C. Grundmann and J. M. Dean, *Angew. Chem.*, **76**, 682 (1964); C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

(9) C. Grundmann and J. M. Dean, *Angew. Chem. Intern. Ed. Engl.*, **4**, 955 (1965).

(10) G. Just and K. Dahl [*Tetrahedron Letters*, 2441 (1966)] studied the oxidation of stereoisomeric aldoximes with lead tetraacetate and found that only the *syn* (*cis*) oximes gave nitrile oxides or products derived from them by secondary reactions.

doximes, the isomers of III are quite stable against alkali; only at 40–60°, far above the preferred temperature range for the hypobromite oxidation, the *anti* oxime is partially rearranged to the *syn* oxime. To account for the facile conversion of the *syn* oxime into the nitrile oxide, we have to assume that the reaction begins with an attack of the oxidant on the negatively charged oxygen atom of the oximate ion which is, as models easily demonstrate, much less sterically hindered than in the *anti* configuration.

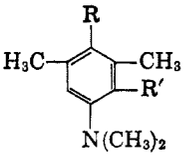
The dioxime of II was obtained only in one configuration which yielded readily the 4-dimethylamino-2,6-dimethylisophthalobisnitrile oxide (VII). Molecular weight determination and infrared spectrum (C≡N stretching at ~2300 cm^{-1}) prove the nitrile oxides IV and VII to be the monomeric compounds. At 25°, these compounds are stable and show no tendency to dimerize to the corresponding furoxans.

Salts of the basic substituted nitrile oxides IV and VII with mineral acids could not be obtained, since the preferred site of attack for the acid was in all cases the nitrile oxide group. For instance, with hydrochloric acid both compounds were first converted into the corresponding hydroxamyl chlorides. The nitrile oxide IV, however, could be quaternized with methyl iodide in an aprotic solvent, such as benzene, to the iodide VIII, which is the first known water-soluble nitrile oxide. Aqueous solutions of VIII are at 0° stable for several days, but at 25° the nitrile oxide is soon reduced by the iodide ion to the corresponding quaternary nitrile (IX). While the oxime III could be easily quaternized with methyl iodide to X, the subsequent oxidation with hypobromite produced for the same reasons only the nitrile IX as the final product. Even when the quaternization of the nitrile oxide IV was carried out in a polar solvent such as methanol, which permits some dissociation of VIII, the internal oxido reduction took place, leading again to the nitrile IX as the sole isolable product. The difunctional nitrile oxide VII did not react at all with methyl iodide. In this case, the tertiary amino group is *ortho* to one of the nitrile oxide groups and apparently there is an interaction of the lone electron pair of the tertiary amino nitrogen with the electrophilic carbon atom of the adjacent nitrile oxide function.

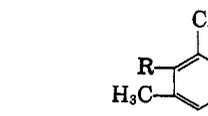
In other reactions, however, the nitrile oxide functions in IV and VII were not affected by the presence of the tertiary amino group. With aniline, the N-phenylamidoximes XI and XII were obtained and the 1,3-dipolar addition of phenylacetylene proceeded normally to the 5-phenylisoxazoles XIII and XIV, as with other sterically hindered, stable aromatic nitrile oxides[8] (Chart I).

Previous attempts to combine the nitrile oxide function with a basic tertiary nitrogen as part of a heterocyclic ring were unsuccessful; failures have been reported in the pyrazole and pyridine series.[3,11–13] As mentioned above, pyridine seems particularly prone to form stable zwitterions with nitrile oxides;[4,6,7] therefore, we concentrated our efforts on the pyrimidine series after preliminary experiments demonstrated this

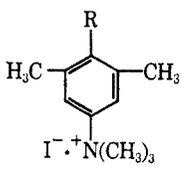
CHART I



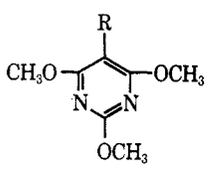
I, R = CHO; R′ = H
III, R = CH=NOH; R′ = H
IV, R = C≡N→O; R′ = H
V, R = CH=NOH; R′ = Br
VI, R = CN; R′ = H
XI, R = C(=NOH)—NHC$_6$H$_5$; R′ = H
XIII, R = C$_6$H$_5$—C=CH; R′ = H



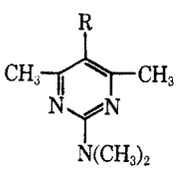
II, R = CHO
VII, R = C≡N→O
XII, R = C(=NOH)—NHC$_6$H$_5$
XIV, R = C$_6$H$_5$—C=CH



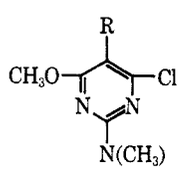
VIII, R = C≡N→O
IX, R = C≡N
X, R = CH=NOH



XV, R = H
XVIII, R = CHO
XXI, R = CH=NOH
XXIV, R = C≡N→O



XVI, R = H
XIX, R = CHO
XXII, R = CH=NOH
XXV, R = C≡N→O
XXVII, R = C(=NOH)NHC$_6$H$_5$



XVII, R = H
XX, R = CHO
XXIII, R = CH=NOH
XXVI, R = C≡N→O

heterocycle to have far less affinity to the CNO group. From the pyrimidines XV, XVI, and XVII the aldehydes XVIII, XIX, and XX were obtained by Vilsmeyer–Haack formylation in the 5 position with N-dimethylformamide–phosphorus oxychloride and converted into the corresponding oximes XXI, XXII, and XXIII.[15] The experimental data of these compounds are summarized in Table I. Dehydrogenation of the oximes XXI–XXIII with alkaline hypobromite gave poor to moderate yields of 2,4,6-trimethoxypyrimidine-5-nitrile oxide (XXIV), 2-dimethylamino-4,6-dimethylpyrimidine-5-nitrile oxide (XXV), and 2-dimethylamino-4-methoxy-6-chloropyrimidine-5-nitrile oxide (XXVI). Molecular weight determinations and

(11) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **25**, 546 (1960).
(12) M. S. Chang and A. J. Matuszko, *ibid.*, **28**, 2260 (1963).
(13) The only known heterocyclic nitrile oxide so far is the 5-methyl-3-phenylisoxazole-4-nitrile oxide, which, however, is devoid of basic properties.[14]
(14) A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **76**, 146 (1946).
(15) The synthesis of pyrimidine-5-aldehydes by the Vilsmeyer–Haack reaction has independently discovered and recently reported by H. Bredereck, G. Simchen, A. Santos, and H. Wagner, *Angew. Chem.*, **78**, 717 (1966); H. Bredereck, G. Simchen, A. A. Santos, *Chem. Ber.*, **100**, 1344 (1967); W. Klötzer and M. Herberz, *Monatsh. Chem.*, **96**, 1567 (1965).

TABLE I

PYRIMIDINE-5-ALDEHYDES, -ALDOXIMES, AND -NITRILE OXIDES

Compd	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
XVII	137	52	$C_7H_{10}ClN_3O$	48.48	5.09	14.14	48.51	5.09	13.91
XIX	151	17	$C_9H_{13}N_3O$	60.31	7.31	23.45	60.29	7.40	23.60
XX	128	88	$C_8H_{10}ClN_3O_2$	44.58	4.66	...	44.83	4.71	...
XXI	248–249[a]	97	$C_8H_{11}N_3O_4$	45.07	5.20	19.71	44.97	5.08	19.64
XXII	144–145	76	$C_9H_{14}N_4O$	55.65	7.27	28.85	55.80	7.43	28.70
XXIII	225	95	$C_8H_{11}ClN_4O_2$	...	...	24.30	...	...	24.60
XXIV	140–142[a]	19	$C_8H_9N_3O_4$	45.50	4.30	19.90	45.54	4.32	20.06[b]
XXV	178–180[a]	34	$C_9H_{12}N_4O$	56.23	6.29	29.15	56.46	6.44	29.00[c]
XXVI	154–155	22	$C_8H_9ClN_4O_2$	42.02	3.95	24.52	42.15	4.07	24.32[d]

[a] With decomposition. [b] Calcd: mol wt, 211. Found: mol wt, 208. [c] Calcd: mol wt, 192. Found: mol wt, 196. [d] Calcd: Cl, 15.51; mol wt, 229. Found: Cl, 15.42; mol wt, 225.

infrared spectra, showing the characteristic strong adsorption around 2300 cm^{-1}, confirmed that the compounds obtained were actually the monomeric nitrile oxides. On storage at room temperature, they did not change over a period of several months. In these compounds, the nitrile oxide function exhibited the usual reactivity; *e.g.*, XXV added aniline to form the N-phenylamidoxime XXVII.

The nitrile oxides IV, VII, VIII, and XXV were evaluated as cytostatics.[16] As with previously tested stable aromatic nitrile oxides, these compounds showed moderate activity in cell culture tests (human epidermoid carcinoma of the nasopharynx), but failed to perform significantly *in vivo*.

Experimental Section[17]

4-Dimethylamino-2,6-dimethylbenzaldoximes (III).—4-Dimethylamino-2,6-dimethylbenzaldehyde[9] (13.8 g) and hydroxylamine hydrochloride (15.0 g) were dissolved in hot methanol (250 ml), 2 *N* NaOH (70 ml) was added, and the methanol was distilled on the steam bath within 2 hr. The residue was diluted with water (100 ml) and the pH was adjusted to 7 with 2 *N* NaOH (30 ml). After standing overnight, the separated crystals were filtered and washed with water to give 14.6 g (97%) of a mixture of the *syn* and *anti* isomers of III, mp 120–132°.

For separation of the isomers, the crude III was recrystallized from methanol (145 ml); the *syn*-4-dimethylamino-2,6-dimethylbenzaldoxime which separated at −10° (11.4 g) was washed with cold methanol, mp 137−138°.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.39; N, 14.67. Found: C, 68.46; H, 8.67; N, 14.57.

The methanolic mother liquors gave, on gradual concentration, subsequent crops of oxime, melting at 126–129° (2.9 g). For further purification these fractions were dissolved at 40–50° in 2 *N* NaOH (290 ml) and filtered from brown impurities, and the *anti*-4-dimethylamino-2,6-dimethylbenzaldoxime was precipitated by adjusting the pH to 7 with acetic acid (~35 g). Small felted needles (2.4 g) were obtained, mp 125°

Anal. Found: C, 68.57; H, 8.37; N, 14.51.

If a solution of the *anti* oxime in 2 *N* NaOH was maintained for several hours at 60–70°, an oily, alkali-insoluble compound separated which was extracted with ether and, after removal of the solvent, recrystallized from aqueous methanol, mp 89°. It proved to be the **4-dimethylamino-2,6-dimethylbenzonitrile** (VI), which could be more easily obtained by heating the *anti* oxime (196 mg) for 5 min with acetic anhydride (5 ml), evaporating the liquid *in vacuo* to dryness, and recrystallizing the residue from aqueous methanol (83% yield). The infrared spectrum shows a medium but very sharp band at 2190 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.00; H, 8.20; N, 15.86.

Neutralization of the above-mentioned alkaline solution of the *anti* oxime after removal of the nitrile yielded the *syn* oxime, mp 136–137°. Thus, alkali rearranges at higher temperatures the *anti* to the *syn* oxime, but under the necessary reaction conditions, the dehydration of the *anti* isomer to the nitrile competes with the rearrangement. The *anti* oxime is apparently the acid-stable form; if the oximation of I was carried out without addition of alkali, the oxime mixture obtained consisted predominantly of the *anti* isomer. However, attempts failed to convert the *syn* oxime back to the *anti* form by treatment with mineral acids.

4-Dimethylamino-2,6-dimethylisophthalodialdoxime.—The dialdehyde II (2.05 g, 10 mmoles) and hydroxylamine hydrochloride (1.70 g) were dissolved on the steam bath in methanol (100 ml), cooled after 5 min to 25°, and neutralized to a pH of 7 by gradual addition of 2 *N* NaOH, then 50 ml of methanol was distilled, and the residue was kept for 2 hr at 0°, filtered, and washed with water. Thus, 2.01 g of a uniform dioxime, mp 177–178° dec, was obtained. One recrystallization from aqueous methanol yielded small needles (1.99 g, 85%), mp 179–180° dec.

Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.14; H, 7.29; N, 17.64.

4-Dimethylamino-2,6-dimethylbenzonitrile Oxide (IV).—The finely pulverized *syn* isomer of III (1.92 g, 10 mmoles) was dissolved by stirring in 2 *N* NaOH (100 ml) at 60–65° and if necessary, filtered from small amounts of undissolved impurities, the filtrate was cooled to 0°, and an ice-cold solution of 1.60 g of bromine in 2 *N* NaOH (11 ml) was added with vigorous shaking within 3–4 min. The finely divided, yellowish precipitate was filtered after 15 min at 25° and washed with distilled water until a colloidal suspension appeared in the filtrate. At this point, it was quickly transferred to a vacuum desiccator and dried as fast as possible over P_2O_5. Prolonged washing of the crude material results in a resinous product from which little nitrile oxide can be obtained. Increasing the size of the batch as well as slight variations in the procedure invariably resulted in poor yields. The crude IV weighs generally between 1.1 and 1.3 g, but the amount of pure IV recoverable may vary widely. Several batches (9.86 g) of this material were combined and recrystallized from ethyl acetate (30 ml), cooled to −10°. A second recrystallization from 10 ml of the same solvent yielded the pure IV in form of thin colorless needles, mp 138–139° dec (15–20% yield).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73; mol wt, 190. Found: C, 69.54; H, 7.54; N, 14.76; mol wt, 191.

During the oxidation of the oxime, a distinctive odor of a lower aliphatic amine (probably dimethylamine) is discernible, indicating concomitant attack of the oxidant at the amine function. From the aqueous, alkaline filtrate of IV after neutralization with acetic acid a mixture of unreacted starting material with some of the brominated oxime V can be recovered by ether extraction. Recrystallization of 3.70 g of this mixture from 20 ml of methanol gave 1.40 g of *syn* III, mp 135°, and from the mother liquor by repeated recrystallization from aqueous acetic acid and then ligroin (bp 60–65°) finally 0.16 g of V, mp 122°, was obtained.

4-Dimethylamino-3-bromo-2,6-dimethylbenzaldoxime (V) is more easily obtained by oxidation of the *anti* oxime III (1.92 g) with hypobromite as described above. The crude, very resinous precipitate and the residue of the ethereal extracts of the neu-

(16) The authors are indebted for this service to the Drug Development Branch of the Cancer Chemotherapy National Service Center, Bethesda, Md.

(17) All melting points were determined with the Fisher-Johns melting point apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular weights were determined by the osmometric method in acetone or chloroform.

tralized mother liquor were purified analogously, yielding 0.3 g V, mp 120°.

Anal. Calcd for $C_{11}H_{15}BrN_2O$: C, 48.72; H, 5.58; Br, 29.47; N, 10.33. Found: C, 48.54; H, 5.51; Br, 29.40; N, 10.15.

4-Dimethylamino-2,6-dimethylisophthalobisnitrile Oxide (VII).—In order to obtain optimum yields of VII it is essential to make the conversion of the dioxime into the bisoximate ion as completely as possible. As with III, larger batches were found to result in very poor yields. 4-Dimethylamino-2,6-dimethylisophthalodialdoxime (1.18 g, 5 mmoles) was dissolved in 10 ml of 4 *N* NaOH and oxidized as described above for the preparation of IV. The average yield from 12 such runs was 42% of crude VII, mp 100–106° dec. The crude product (5.71 g) was dissolved in ethyl acetate (70 ml) at 40–50°, filtered from amorphous flocculent impurities, and concentrated *in vacuo* to 20 ml, and an equal amount of methanol was added. After standing overnight at −10°, 2.25 g of VI had separated in yellowish, stout prisms which were analytically pure after one more recrystallization from benzene–ligroin (bp 60–65°), mp 125–128° with decomposition beginning ~118°.

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17; mol wt, 231. Found: C, 62.19; H, 5.84; N, 17.91; mol wt, 240.

4-Fulmido-3,5-dimethyl-N-trimethylanilinium Iodide (VIII).—The nitrile oxide IV (1.66 g), dissolved in methyl iodide (10 ml) and benzene (30 ml), was refluxed for 48 hr with exclusion of light. After cooling, the separated crystals of VIII (2.40 g, 85%) were filtered off and recrystallized twice from 70 ml of boiling 95% ethanol, yielding broad, slightly pink needles (1.58 g), mp 188° dec.

Anal. Calcd for $C_{12}H_{17}INO$: C, 43.38; H, 5.16; N, 8.43; I, 38.21. Found: C, 43.52; H, 5.31; N, 8.22; I, 37.97.

When the same reaction was carried out in methanol or ethanol, a quaternary iodide (mp 160–174° dec) was obtained, which did not have the CNO band of VIII in the infrared at 2360 cm^{-1}. Repeated recrystallization of this obvious mixture of compounds from aqueous ethanol finally yielded a small amount of **4-cyano-3,5-dimethyl-N-trimethylanilinium iodide** (IX), which is more conveniently obtained from the oxime III. *syn* oxime III (0.56 g) and methyl iodide (1 ml) were dissolved in methanol (15 ml) and left at 25° for 48 hr. After evaporation of the solvent, the residue yielded thick platelets on recrystallization from 10 ml of hot water of **4-formoximino-3,5-dimethyl-N-trimethylanilinium iodide** (X, 0.78 g), mp 196–197°.

Anal. Calcd for $C_{12}H_{19}IN_2O$: I, 37.98. Found: I, 37.78.

Oxidation of X (5.85 g) under the conditions described above for the preparation of IV yielded 1.42 g of the quaternary nitrile IX (besides 2.15 g of unchanged X), which, after two recrystallizations from ethanol–water (1:1), gave pure **4-cyano-3,5-dimethyl-N-trimethylanilinium iodide** (IX) as thin needles, mp 214–215° dec.

Anal. Calcd for $C_{12}H_{17}IN_2$: C, 45.58; H, 5.42; I, 40.14; N, 8.86. Found: C, 45.60; H, 5.52; I, 40.14; N, 8.80.

Reactions of the nitrile oxides IV and VII with aniline or phenylacetylene were carried out as previously described for other nitrile oxides.[8] To obtain the **4-dimethylamino-2,6-dimethylbenzo-N-phenylamidoxime** (XI) in good yield, it is essential that no excess of aniline be used.[18] Recrystallization from methanol yielded 84% of XI in thick platelets, mp 247–248° dec. The amidoxime crystallized with 1 mole of methanol which was removed at 100° (0.1 mm) over P_2O_5 within 3 hr.

Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 71.81; H, 7.53; N, 14.65.

The **4-dimethylamino-2,6-dimethylisophthalobis(N-phenylamidoxime)** (XII) crystallized from aqueous methanol as microscopic prisms (74%), mp 135–136°.

Anal. Calcd for $C_{24}H_{27}N_5O_2$: N, 16.78. Found: N, 16.44.

5-Phenyl-3-(4-dimethylamino-2,6-dimethylphenyl)isoxazole (XIII) crystallized from a little petroleum ether (bp 35–40°) at −10° as broad prisms (42%), mp 76°.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 78.04; H, 6.90; N, 9.58. Found: C, 78.04; H, 7.06; N, 9.59.

4-Dimethylamino-2,6-dimethyl-1,3-di(5-phenylisoxazolyl-3)-benzene (XIV) crystallized slowly as microscopic prisms (81%) from a methanolic solution upon gradual addition of 2 *N* NaOH and scratching. It was purified by extraction with little boiling methanol, mp 171–172°.

Anal. Calcd for $C_{28}H_{25}N_3O_2$: N, 9.65. Found: N, 9.81.

2,4,6-Trimethoxy-pyrimidine (XV) was prepared according to the literature.[19]

2-Dimethylamino-4,6-dimethylpyrimidine (XVI).—The following procedure is preferable to the one given in the literature.[20] Acetylacetone (50 g) and potassium carbonate (138 g) were dissolved in water (250 ml) and 68 g of N,N-dimethylguanidinium sulfate was added and refluxed with stirring for 2 hr. After cooling, 100 g more of potassium carbonate were added and the reaction mixture was left for 48 hr at 25°. The formed oil was separated, combined with the ether extracts of the aqueous phase, and dried over KOH, and the ether was removed by fractional distillation. The residue distills under 15 mm at 90–91° yielding 55 g (73%) of a colorless oil. The picrate (from ethanol) had mp 158° (lit.[20] mp 160–163°).

2-Dimethylamino-4-chloro-6-methoxypyrimidine (XVII).—Sodium metal (4.6 g) was dissolved in methanol (100 ml), a solution of 2-dimethylamino-4,6-dichloro-pyrimidine[21] (9.6 g) in methanol (100 ml) was added, and the mixture was refluxed for 2 hr. After cooling and diluting with twice the volume of water, XVII separated as colorless crystals (87%), which were recrystallized from aqueous methanol, mp 56°.

Anal. Calcd for $C_7H_{10}ClN_3O$: Cl, 18.90. Found: Cl, 18.75.

Formylation of the Pyrimidines XV, XVI, and XVII.—The adduct from $POCl_3$ (0.13 mole) and N,N-dimethylformamide (DMF, 0.3 mole) was formed at 0° as usual. Then the pyrimidine (0.1 mole) was added to the DMF solution. The formylation of XV and XVII required a temperature of 70–80° for 1–1.5 hr, while XVI gave optimum results when the reaction was carried out at 0°, adding the pyrimidine slowly over a period of 20 min, and then stirring the reaction mixture for another 40 min. The formed aldehydes XVIII, XIX, and XX were isolated by dilution with ice water, followed in the case of the strongly basic aldehydes XIX and XX, by careful neutralization with 5 *N* NaOH. The aldehydes thus obtained were sufficiently pure for the subsequent oximation; for analytical purposes, they were once recrystallized from methanol or DMF and water. For further experimental data, see Table I.

Oximation of the Pyrimidine Aldehydes XVIII, XIX, and XX.—To a hot ethanolic solution of the aldehyde (0.1 mole) a concentrated aqueous solution of 0.1 mole of hydroxylamine hydrochloride and the equivalent of Na_2CO_3 was added, and the mixture was heated to a boil for several minutes. The oximes crystallized on cooling; if necessary, the separation was completed by addition of water. Prior to the next step, XXI and XXIII were recrystallized from DMF and water and XXII was isolated from aqueous methanol. Further details concerning these compounds are given in Table I.

Oxidation of the pyrimidine aldoximes XXI, XXII, and XXIII to the pyrimidinenitrile oxides XXIV, XXV, and XXVI was carried out as described in the literature,[9] using procedure B. To achieve complete solution of the oximes XXI and XXIII it was necessary to use 100 ml of 1 *N* NaOH and 3–10 ml of pyridine for 2–5 mmoles of the oxime. Compound XXIV was recrystallized twice from benzene–ligroin (bp 100–110°); XXV and XXVI were purified by recrystallization from methanol. Melting points, yields, and analyses of these compounds are recorded in Table I.

2-Dimethylamino-4,6-dimethylpyrimidine-5-carboxy-N-phenylamidoxime (XXVII).—The nitrile oxide XXV (0.2 g) and aniline (1 ml) were heated for 45 min to 110°, the reaction mixture was diluted with water (10 ml), and the excess of aniline was completely removed by steam distillation under 20 mm. The semisolid residue was crystallized from aqueous methanol yielding 0.12 g (40%) of XXVII, which was recrystallized once again for analysis, mp 168–170°.

Anal. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.55. Found: C, 63.12; H, 6.81; N, 24.26.

Registry No.—*syn* III, 13012-12-9; *anti* III, 13012-13-0; IV, 13012-14-1; V, 13012-15-2; VI, 13012-16-3; VII, 13012-17-4; VIII, 13012-18-5; IX, 13012-19-6; X, 13012-20-9; XI, 13012-21-0; XII, 13012-22-1; XIII,

(18) With an excess of aniline, IV and VII form different compounds which are presently under investigation.

(19) H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 727 (1932); H. Bredereck, A. Bräuninger, D. Hayer, and H. Vollmann, *Chem. Ber.*, **92**, 2937 (1959).

(20) W. Klötzer, *Monatsh. Chem.*, **87**, 131 (1956).

(21) W. R. Boon, *J. Chem. Soc.*, 1532 (1952).

13012-23-2; XIV, 13012-24-3; XVI, 13012-25-4; XVII, 13012-26-5; XIX, 13012-27-6; XX, 13012-28-7; XXI, 13012-29-8; XXII, 13012-30-1; XXIII, 13012-31-2; XXIV, 13012-32-3; XXV, 13012-33-4; XXVI, 13012-34-5; XXVII, 13012-35-6; 4-dimethylamino-2,6-dimethylisophthalodialdoxime, 13012-36-7.

Acknowledgment.—The research of which this publication forms a part was supported by Public Health Service Research Grants CA-07272-93 and -04 of the National Cancer Institute, Bethesda, Md. The authors are indebted to Mrs. J. M. Dean for the preparation of several intermediates.

Flavonoids. III. Studies on the Synthesis of 2,4-Dialkyl-7-acetoxy-4′-methoxy-Δ^3-isoflavenes[1,2]

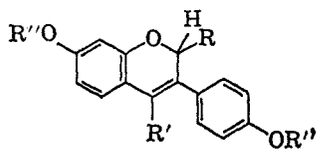
KENNETH H. DUDLEY, ROBERT C. CORLEY, H. WAYNE MILLER, AND MONROE E. WALL

Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received October 18, 1966

A method is described for the conversion of 2-methyl-7-tetrahydropyranyloxy-4′-methoxyisoflavone to 2,4-dialkyl-7-acetoxy-4′-methoxy-Δ^3-isoflavenes. The incorporation of the tetrahydropyranyloxy group, as contrasted with alkyl ether groups, permits a facile cleavage of the protecting group (required for the borohydride reduction step) at a later stage in the synthesis. The synthesis entails the steps: 7-tetrahydropyranyloxyisoflavone → 7-tetrahydropyranyloxyisoflavanol → 7-tetrahydropyranyloxyisoflavanone → 4-alkyl-7-tetrahydropyranyloxyisoflavanol → 4-alkyl-7-hydroxy-Δ^3-isoflavene → 4-alkyl-7-acetoxy-Δ^3-isoflavene.

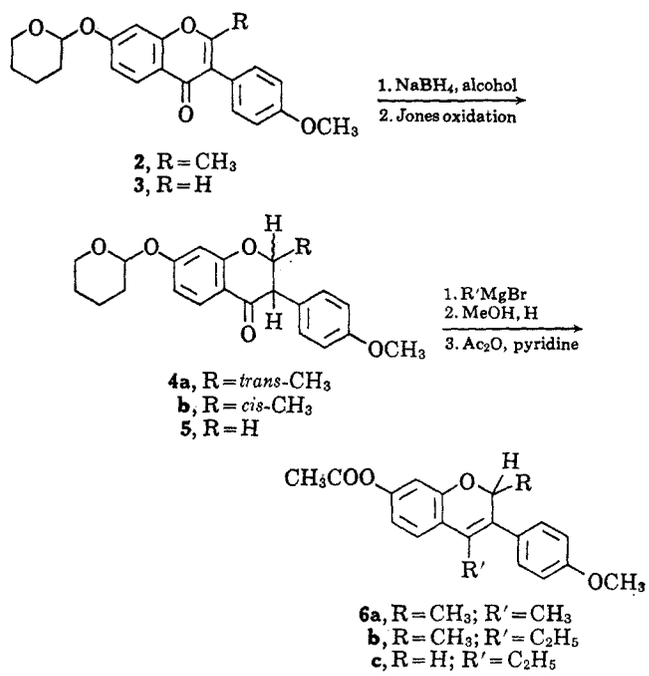
The present study was commenced for the purpose of demonstrating a method of synthetic utility for obtaining 2,4-dialkyl-Δ^3-isoflavenes **1** in the form of free phenols or corresponding acetate derivatives.[3] Previous synthetic endeavors along these lines suffered from low yields[3] or undesirable reactions at the final state of the synthesis.[4]



1

Synthesis of 2,4-Dialkyl-Δ^3-isoflavenes.—The method described here is fundamentally identical with those on record[3,5,6] and involved the steps shown in Scheme I. Because of the difficulties observed with catalytic hydrogenations of isoflavones,[3,7,8] a two-step procedure consisting of exhaustive borohydride reduction[7,9,10] and Jones oxidation was employed for the conversion of isoflavone to isoflavanone. However, a suitable blocking agent was required during the borohydride reduction step, for inhibiting *in situ* conjugate base formation of isoflavone.[11] The tetrahydropyranyl ether group was selected in this synthesis, in view of the

SCHEME I



(1) This research was carried out under Contract SA-43-pH-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

(3) In reviewing the estrogenic activities of flavonoids and the Δ^3-isoflavene problem in general, Micheli, *et al.*, have discussed the biological significance of having Δ^3-isoflavenes in the form of free phenols or the corresponding acetate derivatives: R. A. Micheli, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Med. Chem.*, **5**, 321 (1962).

(4) (a) W. Lawson, *J. Chem. Soc.*, 4448 (1954); (b) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4120 (1965).

(5) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 871 (1953).

(6) C. A. Anirudhan, W. B. Whalley, and (in part) M. M. E. Badran, *ibid.*, 629 (1966).

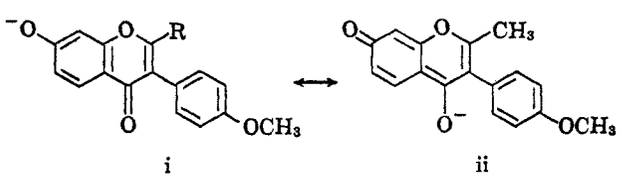
(7) W. D. Ollis in "The Chemistry of the Flavonoid Compounds," T. A. Geissman, Ed., The Macmillan Co., New York, N. Y., 1962, pp 353–405.

(8) During the course of this study, we were unable to confirm the isolation of a 2-methyl-7-acetoxy-4′-methoxyisoflavanone, mp 176–179° (*cf.* ref 5), by the catalytic hydrogenation of 2-methyl-7-acetoxy-4′-methoxyisoflavone. The compound of Bradbury and White, mp 176–179°, would undoubtedly be the *cis* derivative, for which we obtained mp 71–81° and mp 80–83° (best sample).

(9) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958).

(10) (a) L. R. Row, A. S. R. Anjaneyulu, and C. S. Krishna, *Current Sci.* (India), **32**, 67 (1963); (b) A. S. R. Anjaneyulu, C. S. Krishna, and L. R. Row, *Tetrahedron*, **21**, 2677 (1965).

(11) The failure of 2-methyl-7-hydroxy-4′-methoxyisoflavone and 7-hydroxy-4′-methoxyisoflavone (or the corresponding 7-acetoxy and 7-trimethylsilyloxy derivatives) to undergo reduction by alcoholic borohydride solution is undoubtedly due to salt formation *in situ*. Anion formation (i ↔ ii) would be expected to lessen the susceptibility of the α,β-unsaturated ketone system to hydride attack. In these cases, under normal and strenuous conditions, the 7-hydroxyisoflavone derivatives were observed (tlc), and reisolated, as sole reaction components (authors' unpublished experiments).



i ii

(12) J. F. W. McOmie in "Advances in Organic Chemistry: Methods and Results," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1963, p 191.