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SYNTHESIS, REACTIONS, AND PROPERTIES OF SOME HIGHLY HINDERED DIPHENYL ETHERS[1, 2]

MARJORIE ALLEN[3] AND R. Y. MOIR

ABSTRACT

In the Hems synthesis of diphenyl ethers, an ortho-carbonyl offered less obstruction when held in a lactone ring than when present as an ester. Side reactions interfered with the Hems synthesis of highly hindered diphenyl ethers, and the highly hindered, highly activated ethers produced in the synthesis were easily cleaved by nucleophilic reagents, often in a few minutes at room temperature. The latter fact added a lively interest to the transformation of the ethers into other derivatives. Three of these were of special interest: (*a*) methyl 2-(6′-amino-4′-carbomethoxy-2′-nitrophenoxy)benzoate (VI*c*) which existed in remarkably stable dimorphic forms, (*b*) the dibenzoxazepine VIII, and (*c*) the quadruply orthosubstituted, asymmetrical 7-(4′-carbomethoxy-6′-laevo-menthoxyacetamino-2′-nitrophenoxy)metameconine (IX). Attempts to isolate diastereoisomeric substances having the diphenyl ether link as an element of asymmetry failed, the classical explanation of the low configurational stability (due to bending and twisting of bonds) being superior to the quantum mechanical explanation of a tunnelling oscillation of oxygen.

This paper describes the synthesis of diphenyl ethers bearing three or four groups ortho to the ethereal linkage, their conversion into asymmetrical derivatives, and our tentative conclusion that the unsymmetrical derivatives cannot be resolved into optical isomers at room temperature. The most interesting part of the paper describes the synthetic methods that must be used in the face of the very great ease of disruption of the ethereal linkage.

Synthesis of Hindered Diphenyl Ethers

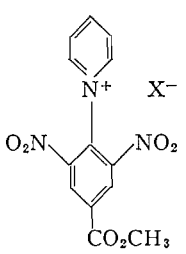
Ullmann's reaction (1, 2) is not very useful for the synthesis of hindered diphenyl ethers[4] (3, 4, 5, 6, 7, 8, 9). A more powerful method is the well-known reaction of a phenol, a base, and an activated aryl halide (10, 11, 12). Considerable activation is required in the aryl halide: with low activation, as with *p*-fluoronitrobenzene, the reaction occasionally fails with as few as two ortho substituents (13), but with greater activation successes with three ortho groups are common, and using the great activation of picryl chloride, Dahlgard and Brewster (14) recently succeeded in making two quadruply orthosubstituted diphenyl ethers. In this method, the large number, position, and similarity of the activating groups required are an embarrassment in further synthetic steps. A more promising synthesis discovered by Borrows, Clayton, Hems, and Long (15) has as its essential step the reaction of a phenol with an activated N-phenylpyridinium salt.

One main advantage of the new method is its lower requirements for activation (9, 15). The discoverers of the reaction felt that at least two nitro groups were required, but

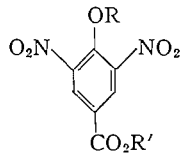
[1]*Manuscript received July 6, 1959.*
Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario.
[2]*Most of the material is taken from a thesis written by Mrs. Marjorie Allen at Queen's University in April, 1959, in partial fulfillment of the requirements of the degree of Master of Arts. Some (referred to this footnote) is taken from a paper given by R. Y. Moir at the Symposium in Organic Chemistry of the Chemical Institute of Canada at Montreal, March 9, 1954.*
[3]*Canadian Industries, Limited, Fellow, 1958–59.*
[4]*See footnote 2.*

McRae, Moir, Ursprung, and Gibbs (9) and at almost the same time Grundon and Perry (16) showed that activation by one nitro and one carbomethoxy group sometimes sufficed. Constantin and L'Écuyer (17) later showed that one nitro and one formyl group were sufficient in several instances. This theoretically small extension of the limits of activation has already been of considerable service to those interested in the synthesis of cularine and the bis-benzylisoquinoline alkaloids (9, 16, 17, 18).

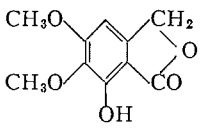
The new synthesis may produce highly hindered diphenyl ethers with fantastic ease from moderately activated reactants. Thus N-(4-carbomethoxy-2,6-dinitrophenyl)-pyridinium chloride (I*a*) with 7-hydroxymetameconine[5] (III) gave the maximally orthosubstituted ether IV*a*, while the slightly activated N-(4-carbomethoxy-2-



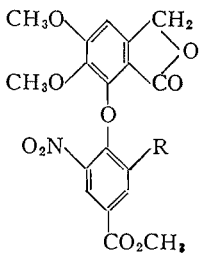
I*a*: $X^- = Cl^-$
I*b*: X^- = Anion of II*a*



II*a*: R = H; R′ = CH_3
II*b*: R = R′ = H
II*c*: R = R′ = CH_3

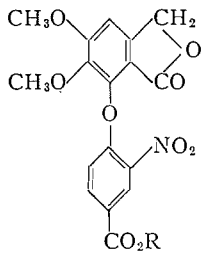


III

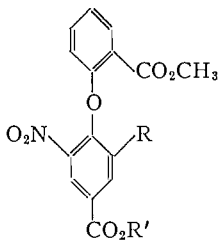


IV*a*: R = NO_2
IV*b*: R = NH_2
IV*c*: R = NHOAc

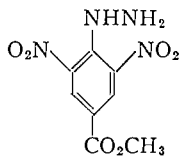
nitrophenyl)pyridinium tosylate reacted easily with III to give the triply orthosubstituted ether V*a* (9). In this paper it is shown that I*a* reacts with methyl salicylate to give the triply orthosubstituted ether VI*a* with ease. Nevertheless, since 1952 we have accumulated many more failures than successes with the method. For example, methyl salicylate, which smoothly reacts with I*a*, has repeatedly failed to react with the less activated N-(4-carbomethoxy-2-nitrophenyl)pyridinium tosylate, which in turn reacts smoothly with III. These examples must closely illustrate the lower limit of activation for ortho-carbomethoxydiphenyl ethers (compare reference 17).



V*a*: R = CH_3
V*b*: R = H



VI*a*: R = NO_2; R′ = CH_3
VI*b*: R = NO_2; R′ = H
VI*c*: R = NH_2; R′ = CH_3
VI*d*: R = NHOAc; R′ = CH_3



VII

One new side reaction is conveniently described here. In the new preparation of VI*a*, as well as in the repetition of the synthesis of IV*a*, the same quaternary salt, N-(4-carbomethoxy-2,6-dinitrophenyl)pyridinium 4′-carbomethoxy-2′,6′-dinitrophenoxide (I*b*) was

[5]*The numbering scheme for the metameconines is that of Chemical Abstracts. A different scheme was used in our previous papers in this journal.*

isolated in considerable yield. Its proof of structure by synthesis and degradation is described in the experimental part. Quaternary salts have previously been isolated from two sources in the synthesis: (*a*) from a simple double decomposition of the ionic reactants, or (*b*) from a nucleophilic attack of pyridine upon an activated diphenyl ether (the reverse of the synthetic reaction) (19). The salt I*b* must have arisen in still a third way, the simplest explanation being that it arose from the hydrolysis of the very unstable reactant I*a*, probably during the isolation of the products. If this explanation is correct, then water attacks I*a* at the 1-position of the benzene ring, while hydroxide ion attacks it at the 2-position of the pyridine ring (see Experimental section) (20), a conclusion that raises the most interesting questions about the mechanism of the synthesis.

Other side reactions will be reported in a later paper, together with the limitations they set upon the scope of the synthesis.

Reactions of Highly Hindered, Highly Activated Diphenyl Ethers

Nucleophilic scissions of the ethers described in this paper occur with remarkable rapidity; apparently a considerable energy of steric compression aids the well-known effects of activation (11). The experimental methods described below were designed to avoid disruption of the sensitive ethereal linkages while (*a*) introducing asymmetry into the molecules or (*b*) hydrolyzing ester groups to free carboxyl groups with a view to possible resolutions.

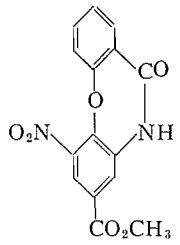
The ether V*a* is readily cleaved by alkali (9) but careful control of the conditions of saponification has now been found to give the free acid V*b* in very high yield and purity. With the more highly activated ether VI*a*, good yields on saponification were no longer possible. The best yields of the free acid VI*b* were given by 5 minutes' contact of VI*a* with aqueous potassium hydroxide at room temperature; scission of VI*a* was easily detectable after only 1 minute's contact! The conditions which served to give excellent yields in the saponification of V*a* completely degraded VI*a* to the phenolic acid II*b*.

With more nucleophilic reagents it was not possible to prevent nucleophilic attack upon the ether. Methoxide ion (provided by barium hydroxide in methanol) degraded VI*a* *without* saponification to the ester II*c* in 3 minutes at room temperature. (The reagent was shown to be capable of saponifying II*a* to the barium salt of II*b*.) Hydrazine and Raney nickel gave the phenylhydrazine VII without concurrent reduction of the nitro groups.

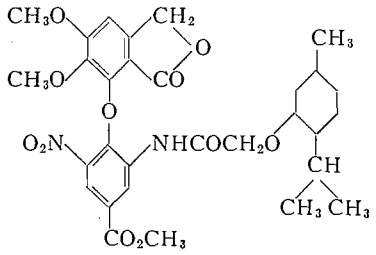
Selective reduction of one nitro group was achieved with iron and acetic acid. The ether IV*a* was reduced to IV*b*, and the ether VI*a* to VI*c*. These very fortunate reductions provided the asymmetry needed for possible resolvability. Each of the amino esters was characterized through its acetyl derivative (IV*c* and VI*d*, respectively). The amino ester VI*c* exhibits a dimorphism remarkable in that both forms sometimes crystallize together spontaneously from the same mother liquor. The very reproducible double melting point is shown in Plate I.

When the amino ester VI*c* was heated to 210°, it was converted into its lactam (VIII), which was also produced more directly by the reduction of the dinitro ester VI*a* with stannous chloride in the presence of hydrochloric acid. The interesting ring system of VIII (21) is accompanied by substituents well placed for further synthesis. It might be added that the formation of VIII and of the monoacetyl derivatives IV*c* and VI*d*, the scissions of the ethers, and the methods of synthesis provide unequivocal proofs of the structures suggested in this paper and the previous one (9).

The amino ester IV*b* was converted into its N-laevo-menthoxyacetyl derivative IX, the farthest step in our development of the chemistry of metameconine (8, 9, 22), and the most highly hindered asymmetrical diphenyl ether we have yet been able to produce.



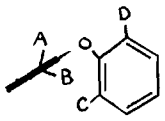
VIII



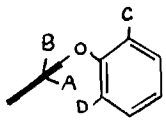
IX

Resolvability of Highly Hindered Diphenyl Ethers

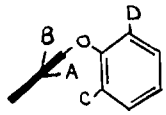
Many years ago it was suggested[6] on the basis of a study of models (9) that suitably hindered diphenyl ethers might be resolvable into optical isomers. During the course of our work, Dahlgard and Brewster (14) reported their failure to resolve an unspecified highly substituted diphenyl ether. They further suggested that such a resolution might be theoretically impossible if there exists a "tunnelling" oscillation of the ethereal oxygen analogous to the oscillation that destroys asymmetry in substituted ammonias. That was not our independent appraisal of the problem, and a study of the models shows that inversion with the allowed rotations converts a diphenyl ether into itself.



X



XI



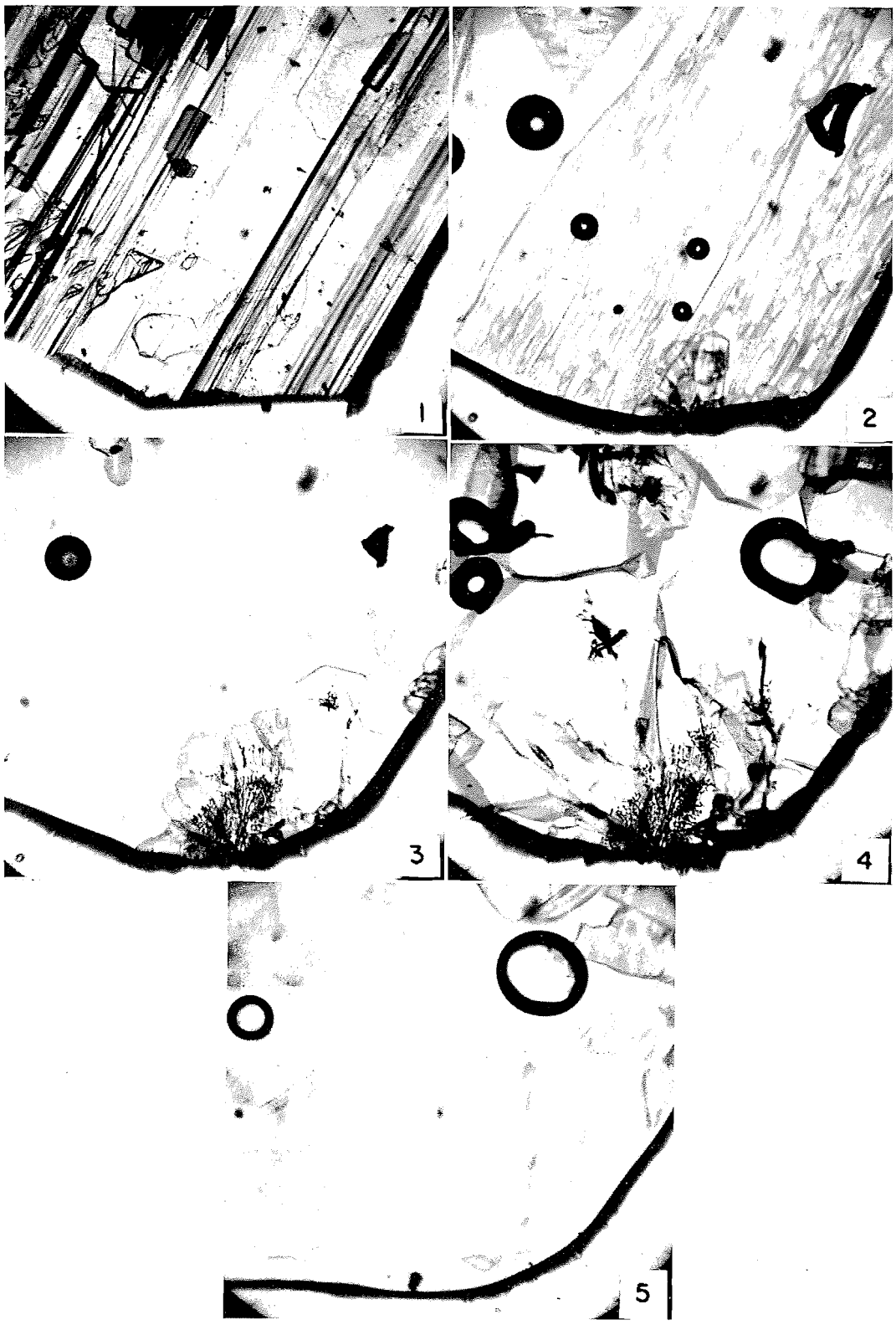
XII

In compound X, A is behind the plane of the paper, and B is in front. Inversion through oxygen converts X into XI, while concerted rotation of the two benzene rings about the oxygen bonds converts XI into X. Neither X nor XI can be made to coincide with XII, the mirror image of X, unless interfering groups are forced past each other.

However, we have failed to separate into diastereoisomers either the brucine salt of V*b*, or the much more highly hindered amide IX. Moreover, neither of these compounds exhibited any mutarotation in solution, so that apparently even the lower order of configurational stability, observed by Adams and his co-workers (23) for slightly hindered diphenyls, is absent. Dahlgard and Brewster (14) showed that increasing orthosubstitution of diphenyl ethers is accompanied by the gradual disappearance of absorption bands near 3000 Å in the ultraviolet spectra. They felt that this was due to the growing lack of coplanarity between the benzene rings with the consequent loss of quininoid resonance, and they concluded that rotational isomers of diphenyl ethers do exist, though they may not be sufficiently stable to be isolated as such. The triply orthosubstituted ether V*a* showed marked absorption near 2900 Å, while the maximally orthosubstituted ethers VI*c* and IX showed only very weak bands near 3550 Å and 3250 Å, respectively. Accepting the interpretation of Dahlgard and Brewster does lead to the reasonable conclusion that

[6]*See footnote 2.*

FIGS. 1–5. Dimorphism of methyl 2-(6′-amino-4′-carbomethoxy-2′-nitrophenoxy)benzoate (VI*c*).
FIG. 1. "Plate" form at room temperature. FIG. 2. "Plate" form melting at 135°, with the "prism" form already beginning to grow in the melt. FIG. 3. Growth of "prism" form, 136–141°. FIG. 4. Complete solidification at 141°. FIG. 5. Melting of "prism" phase at 144–145°. (Photomicrographs by Professor J. R. Allen.)



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there is little steric interference with coplanarity in V*a*, but that there is marked interference in VI*c* and IX.

EXPERIMENTAL

Melting points, unless otherwise stated, were determined in an instrument of high precision (24). Melting points followed by (k) were performed on a Koffler Micro Hot Stage and lowered 3–5° to agree with precision capillary melting points within less than 1° up to 250°. Uncorrected melting points were determined in the Fisher–Johns apparatus; comparison with the precision apparatus at one point near the center of the range used here showed the instrument to read about 3° high. Infrared spectra with one exception were done with potassium bromide disks containing 0.8% to 2% by weight of the sample. Ultraviolet spectra were determined with the Beckman recording spectrophotometer. Pyridine was heated under reflux with barium oxide, distilled from the barium oxide, and stored over fresh barium oxide.

7-(4'-Carbomethoxy-2'-nitrophenoxy)metameconine (V*a*)

A repetition of the previous procedure (9) showed that no by-product of the type described below (see under IV*a*) could be isolated.

7-(4'-Carboxy-2'-nitrophenoxy)metameconine (V*b*)

The methyl ester (V*a*) (5.52 g) was mechanically stirred at 76–81° for 30 minutes with a solution of potassium hydroxide (2.9 g) in water (30 ml) and 95% ethanol (30 ml). The solution was immediately cooled and acidified; the fine needles which slowly deposited were recovered, washed, and dried; yield 88%, m.p. 236.0–237.8°. Two recrystallizations from dilute acetic acid gave the analytical sample of V*b*, m.p. 237.4–238.4°, in agreement with the indirectly characterized material previously obtained (9). Found: C, 54.28; H, 3.52%. Calc. for $C_{17}H_{13}O_9N$: C, 54.40; H, 3.49%.

The *brucine salt* of this acid was subjected to three lengthy fractional crystallizations from acetone and from methanol; the salt fractions all showed similar, wide, melting ranges with unsatisfactory upper limits, and their habits varied. A typical fraction of the salt (3.03 g) had m.p. 174.5–177.5° (uncorr.), and $[\alpha]_D^{21} = -7°$ (in chloroform), with no mutarotation at all in the period of 4 to 71 minutes after formation of the solution. Free acid was liberated from the salt by very cautious acidification in the cold of initial, central, and final fractions, but all the acid fractions had zero rotation. Attempts were also made to induce spontaneous crystallization of one enantiomorph of the free acid, using new apparatus free from scratches, great precautions to destroy random seeds, and seeding from single, well-formed crystals with early interruption of the recrystallization process, but all the attempts gave acids of zero rotation.

7-(4'-Carbomethoxy-2',6'-dinitrophenoxy)metameconine (IV*a*)

A repetition of the previous experiments (9) showed the presence of a by-product. Methyl 4-chloro-3,5-dinitrobenzoate (I*a*) (1.65 g) (15) and dry pyridine (10 ml) were warmed on the steam bath for 5 minutes, the pyridinium salt separating as crystals. 7-Hydroxymetameconine (III) (1.35 g, m.p. 158–159°) (9) was added and the heating continued for 90 minutes. The deep red solution was poured onto ice and the product, which soon solidified, was recovered, dried, and recrystallized from acetone to give a mixture of (*a*) pale yellow prisms, and (*b*) long, deep yellow needles. The products were separated mechanically by swirling away the lighter needles in the acetone mother liquor, a process which greatly simplified the subsequent purifications. After a second recrys-

tallization from acetone the prisms gave 1.4 g of pure 7-(4′-carbomethoxy-2′,6′-dinitrophenoxy)metameconine (IV*a*), m.p. 210–211° (k). Found: N, 6.55%. Calc. for $C_{18}H_{14}N_2O_{11}$: N, 6.45%. The crystals were stable in air (cf. ref. 9), but they were decomposed by light.

The yellow needles, after another recrystallization from acetone, melted at 240–242° (uncorr.). They are shown below to be N-(4-carbomethoxy-2,6-dinitrophenyl)pyridinium 4′-carbomethoxy-2′,6′-dinitrophenoxide (I*b*).

7-(6′-Amino-4′-carbomethoxy-2′-nitrophenoxy)metameconine (IV*b*)

Iron powder (0.27 g) was heated on the steam bath for 1 hour with a solution of 7-(4′-carbomethoxy-2′,6′-dinitrophenoxy)metameconine (IV*a*) (1.0 g) in glacial acetic acid (60 ml). The mixture was evaporated to dryness and the residue thoroughly extracted with water and then with boiling methanol (100 ml). A yellow powder (0.4 g), m.p. 230–233° (k) was thus obtained; two recrystallizations from acetone gave the analytical sample, m.p. 234–235° (k). Found: C, 53.63; H, 3.99; N, 7.18%. Calc. for $C_{18}H_{16}O_9N_2$: C, 53.47; H, 3.96; N, 6.93%.

7-(6′-Acetamino-4′-carbomethoxy-2′-nitrophenoxy)metameconine (IV*c*)

The above amino compound (IV*b*) (0.1 g) was heated 5 minutes with acetic anhydride (2 ml) and concentrated sulphuric acid (1 drop). The solution was poured into water and boiled to decompose the acetic anhydride. White needles, m.p. 197–199° (k) were deposited from the cooled solution. Two crystallizations from 50% aqueous methanol raised their m.p. to 206–207° (k). Found: C, 54.16, 54.14; H, 4.14, 4.02; N, 6.08, 6.50%. Calc. for $C_{20}H_{18}O_{10}N_2$: C, 53.81; H, 4.04; N, 6.28%.

7-(4′-Carbomethoxy-6′-laevo-menthoxyacetamino-2′-nitrophenoxy)metameconine (IX)

The amino compound IV*b* (0.539 g), laevo-menthoxyacetyl chloride (0.31 g), $[\alpha]_D = -85.75°$ (*c*, 2.13 in chloroform) (25), and chloroform (30 ml) were heated under reflux for 6 hours. The crystals (0.1 g) which separated from the cooled solution had a m.p. of 228–232° (k), undepressed by admixture with authentic IV*b*. Evaporation of the mother liquors and trituration of the oily residue with petroleum ether gave a solid, which was sensitive to light, in a yield of 0.7 g, m.p. 183°. Five successive recrystallizations gave products of the following melting points (k): (from ethanol) 185–190°; (from ethanol) 188–191°; (from methanol) 188–190°; (from benzene – petroleum ether) 188–190°; (from ethanol) 188–189°; thus there was no evidence for the presence of stable diastereoisomers. Stout white needles. Found: C, 60.23; H, 6.08; N, 4.85%. Calc. for $C_{30}H_{36}O_{11}N_2$: C, 60.00; H, 6.00; N, 4.67%.

A solution of the menthoxy-amide (IX) (0.1467 g) in chloroform (solution volume 5 ml) was observed in the polarimeter; nine readings were taken over the period from 5 minutes to 68 hours after the formation of the solution, each reading, as well as the instrument's zero-point, being the mean of 10 observations. The corrected readings varied smoothly from the initial value of −0.85° to the final value of −0.89°; the variation was probably not significant. The initial value gives $[\alpha]_D = -29°$ and a molar rotation of −174°; under approximately the same conditions the molar rotation of purified menthoxyacetic acid was found to be −190°. The lack of mutarotation, and the approximate agreement of the molar rotations, were regarded as significant.

Methyl 2-(4′-Carbomethoxy-2′,6′-dinitrophenoxy)benzoate (VI*a*)

Methyl 4-chloro-3,5-dinitrobenzoate (2.6 g) and dry pyridine (15 ml) were heated

5 minutes on the steam bath. Methyl salicylate (1.5 ml) was then added and the heating continued for 90 minutes. The dark colored solution deposited a bright yellow gum on being poured onto ice (100 g); when the gum had solidified it was recovered, washed with water, and dried. The crude mixed product was separated into its components in any of three ways.

(*a*) Recrystallization from acetonitrile gave bright yellow needles, m.p. 241–242° (uncorr.) in a yield of 0.4 g, or 11%. Evaporation of the mother liquors followed by recrystallization of the residue from ethanol gave the diphenyl ether VI*a*, m.p. 109.5–110.5°, yield 2.1 g (56%). One more recrystallization from ethanol gave the analytical sample, m.p. 110.6–111.2°. Found: C, 51.12; H, 3.50; N, 7.71%. Calc. for $C_{16}H_{12}O_9N_2$: C, 51.06; H, 3.22; N, 7.45%.

(*b*) Extraction with hot ethanol left the yellow needles undissolved; the ether was recovered by dilution of the ethanol. Further recrystallizations gave the same two products as before.

(*c*) The crude product was washed with dilute hydrochloric acid (which decomposed the yellow needles) and then recrystallized twice from ethanol to give the pure ether, m.p. 110–111°. On a larger scale, 23.3 g (73% of theory) of the twice recrystallized ether VI*a*, m.p. 110–111°, was made in this more convenient way.

The yellow needles are shown below to be N-(4-carbomethoxy-2,6-dinitrophenyl)-pyridinium 4′-carbomethoxy-2′,6′-dinitrophenoxide (I*b*).

Stability of Methyl 2-(4′-Carbomethoxy-2′,6′-dinitrophenoxy)benzoate (VI*a*) *in Pyridine*

The dinitroether VI*a* (0.5 g) and dry pyridine (5 ml) were heated on the steam bath for 30 minutes, poured onto ice, the precipitate recovered and recrystallized from methanol. The product (0.4 g) had m.p. 111°, undepressed by admixture with the original ether. Hence the quaternary salt (I*b*) did not arise from nucleophilic attack upon the diphenyl ether.

Scissions of the Diphenyl Ether Linkage; Preparation of Methyl 2-(4′-Carboxy-2′,6′-dinitrophenoxy)benzoate (VI*b*)

(*a*) *With Hot Potassium Hydroxide*

The dimethyl ester VI*a* (0.3 g) was heated under gentle reflux for 30 minutes with 10% aqueous potassium hydroxide solution. The cooled, acidified solution deposited white crystals, m.p. 254–255° (uncorr.). Analyses were approximately correct for 3,5-dinitro-4-hydroxybenzoic acid (II*b*), and the identification was confirmed by mixture melting point with authentic material (made by saponification of the methyl ester II*a*, and twice recrystallized from ethanol; the melting point of 254–255° (uncorr.) was considerably higher than that (244–246°) observed by Christianson) (26).

(*b*) *With Cold Potassium Hydroxide*

The dimethyl ester VI*a* (3.0 g) was dissolved in hot ethanol and the solution rapidly cooled to give a suspension of very fine crystals. Potassium hydroxide solution (18 ml of 10%) was slowly added and the mixture shaken at room temperature for 5 minutes. Ether (50 ml) was then added, and the mixture acidified, separated, and the aqueous layer extracted with three 50-ml portions of ether. Exhaustive back extraction of the combined ethereal layers with cold sodium bicarbonate solution (each extract being rapidly chilled and acidified after the extraction) followed by re-extraction with ether of the acidified sodium bicarbonate extracts, and evaporation of the final, dried, ethereal extracts, gave a pale yellow oil containing some crystals. Recrystallization of the oily mixture from methanol gave 1.1 g of light-sensitive crystals m.p. 175–185°. Three more

wasteful recrystallizations from methanol gave the analytical sample of 2-(4′-carboxy-2′,6′-dinitrophenoxy)benzoate, m.p. 214–215° (k). Found: C, 49.81; H, 2.90; N, 7.62%. Calc. for $C_{15}H_{10}O_9N_2$: C, 49.72; H, 2.76; N, 7.74%.

When a similar preparation was acidified after the reaction had proceeded for only 1 minute at room temperature, a strong odor of methyl salicylate could be detected. This observation, together with the isolation of the free dinitro acid (II*b*) in (*a*) part, and the rapid saponification observed in the less activated ether (V*a*) (see above), made it sufficiently clear that it was the less activated ester group which remained in compound VI*b*.

(*c*) *With Acids*

When the dimethyl ester VI*a* was heated under reflux with dilute acetic acid containing a little *p*-toluenesulphonic acid, it was recovered unchanged almost quantitatively. An attempted transesterification with glacial acetic acid and *p*-toluenesulphonic acid gave no detectable methyl acetate in the fractionating column, and again the recovery of unchanged material was almost quantitative. When concentrated sulphuric acid was allowed to react with the ester at room temperature for 14 hours, and the mixture poured into water, recovery of the starting material was lower, and a strong odor of methyl salicylate showed that some rupture of the ethereal linkage had occurred.

(*d*) *With Methoxide Ion*

The dimethyl ester VI*a* (2 g) was dissolved in a methanolic solution of barium hydroxide hydrate (64 ml of a solution containing 18 g of the hydrate per liter) and allowed to react for 3 minutes at room temperature. No precipitate formed. The deep red solution was then acidified, diluted with water, and extracted with ether. The ethereal extracts were dried and evaporated; the yellow oil remaining (1.7 g) had a strong odor of methyl salicylate. Extraction of an ethereal solution of the oil with aqueous sodium bicarbonate, removal of the ether, and recrystallization of the residue from methanol gave white crystals in a yield of 0.6 g, whose m.p. of 54–55° was not depressed by admixture with authentic methyl 3,5-dinitro-4-methoxybenzoate (II*c*) (prepared by the action of diazomethane upon II*a*, and recrystallized from methanol, m.p. 52–53°).

Methyl 3,5-dinitro-4-hydroxybenzoate (II*a*) (1 g) was dissolved in 150 ml of the same solution of barium hydroxide hydrate in methanol, and allowed to stand 3 days at room temperature. The bright orange crystals (1.7 g) of the barium salt were recovered, suspended in water (150 ml), and acidified; the free acid slowly precipitated and on recovery it had a m.p. of 249–250° (uncorr.) undepressed by admixture with authentic II*b*. Thus the scission of the ether had been accomplished by direct nucleophilic attack of methoxide, and not, for example, by hydrolysis followed by methylation of the free phenolic group by the activated methyl ester.

(*e*) *With Hydrazine*

The dimethyl ester VI*a* (1 g) was suspended in absolute alcohol and treated with a solution of hydrazine hydrate (0.4 g) in ethanol (2 ml). A little Raney nickel was added and the mixture heated under reflux for 1 hour, more ethanol being added to keep the product in solution. The hot solution was filtered from the Raney nickel and cooled; the red crystals (0.3 g) which separated were recovered and thrice recrystallized from ethanol to give thick red needles of 4-carbomethoxy-2,6-dinitrophenylhydrazine (VII), m.p. 171° (k). Found: C, 37.58; H, 3.26; N, 22.03%. Calc. for $C_8H_8O_6N_4$: C, 37.51; H, 3.12; N, 21.87%. The phenylhydrazine reacted with benzaldehyde to give a derivative which on purification consisted of orange plates, m.p. 241° (k), not further characterized.

Methyl 2-(6'-Amino-4'-carbomethoxy-2'-nitrophenoxy)benzoate (VI*c*)

The dinitro ester VI*a* (1 g) was dissolved in glacial acetic acid (25 ml) and gently warmed to 30° with iron powder (0.45 g). The temperature then rose spontaneously to 55° and was kept at 50–55° for 15 minutes by external cooling. Allowed to cool by itself during 30 minutes more, the mixture was then filtered from a precipitate which was washed with hot glacial acetic acid. The combined filtrates were evaporated to dryness, the residue thoroughly extracted with ether, the ether evaporated, and the residual oil recrystallized from methanol with charcoal to give 0.5 g of yellow crystals, m.p. 134–138°. Five successive recrystallizations from methanol gave crystals of grossly erratic shape and melting point. In a second preparation, the product was recrystallized once from methanol and then five times from benzene, with the same erratic results (which were therefore not due to solvent of crystallization) (see below). The final analytical sample so obtained consisted of needles, m.p. 135° (k). Found: N, 8.16%; and on another sample: C, 55.67, 55.63%; H, 4.08, 3.92%. Calc. for $C_{16}H_{14}O_7N_2$: C, 55.49; H, 4.08; N, 8.09%.

Dimorphism of Methyl 2-(6'-Amino-4'-carbomethoxy-2'-nitrophenoxy)benzoate (VI*c*)

The analytical sample of the amino ester VI*c* (0.2 g, m.p. 139°) was heated at 150° for 45 minutes to give a clear yellow melt without any signs of decomposition. Allowed to cool slowly, the melt produced crystals of m.p. 141–143°; admixture with the starting material gave an intermediate m.p. of 137–139°. Recrystallization of the solidified material from methanol gave a mixture of crystals of two distinct forms: (*a*) pale yellow "prisms" (*b*) slightly darker yellow "plates". The two forms were separated by hand, and careful examination of the prisms (type "*a*") under the microscope showed them to be perfectly free from crystals of type "*b*". Nevertheless, recrystallization of the prisms from methanol gave plates of type "*b*". Careful heating of these plates on the hot stage of the microscope showed melting to begin at 135°; at 137° crystals of the prism type "*a*" appeared in the melt, and at 139° the sample had solidified entirely into the prism form, which then melted at 144–145°. This sequence, remarkable for its reproducibility, has twice been recorded photomicrographically by Professor J. R. Allen, as shown in Plate I.

Infrared spectra of the solid plates and prisms in potassium bromide disks showed differences in the regions of 1300 to 1375 cm^{-1}, and 3280 to 3300 cm^{-1}, but the infrared spectra of chloroform solutions of the two forms were identical.

Methyl 2-(6'-Acetamino-4'-carbomethoxy-2'-nitrophenoxy)benzoate (VI*d*)

The amino ester VI*c* (0.1 g, m.p. 142°), acetic anhydride (1 ml), and concentrated sulphuric acid (1 drop) were heated together to complete solution, then diluted with water (20 ml) and heated to destroy the acetic anhydride. When cool, the solution deposited pale yellow needles which after four recrystallizations from aqueous ethanol gave the colorless analytical sample m.p. 149–150° (k). Found: C, 55.43, 55.29; H, 4.19, 4.29; N, 7.75%; on another sample: N, 7.14, 7.35%. Calc. for $C_{18}H_{16}O_8N_2$: C, 55.68; H, 4.12; N, 7.22%.

8-Carbomethoxy-6-nitro-11-oxo-10,11-dihydro-dibenz[b,f][1,4]oxazepine (Lactam of 2-(6'-Amino-4'-carbomethoxy-2'-nitrophenoxy)benzoic Acid (VIII)

(*a*) The amino ester VI*c* (0.2 g, m.p. 135°) was heated in an oil bath at 210° for 30 minutes. Decomposition was evident, and the cooled melt was a black tar coated with white crystals. Extraction with hot methanol left the white crystals as an insoluble residue, m.p. 315–316° (k).

(*b*) The dinitro ester VI*a* (0.5 g), dissolved in glacial acetic acid (15 ml), was heated for

30 minutes on the steam bath with a solution of stannous chloride dihydrate (1.0 g) in concentrated hydrochloric acid (2 ml). White needles were recovered from the cooled reaction mixture; one recrystallization from glacial acetic acid gave 0.1 g of fluffy needles, m.p. 289–291° (uncorr.), and two more similar recrystallizations gave the analytical sample, m.p. 315–316° (k). Found: C, 57.75; H, 3.59; N, 8.83%. Calc. for $C_{15}H_{10}O_6N_2$: C, 57.32; H, 3.19; N, 8.92%. The melting point was not depressed by admixture with the product from (*a*), and the infrared spectra of the two preparations were identical.

Supposed N-(*4'-Carbomethoxy-2',6'-dinitrophenyl*)*pyridinium Chloride* (I*a*)

Methyl 4-chloro-3,5-dinitrobenzoate (2.6 g) (15) in dry benzene (20 ml) was treated with dry pyridine (1.5 ml). After 1 hour the slightly sticky yellow crystals were recovered, washed with benzene and then with acetone, dissolved in warm ethanol, and reprecipitated with ether to give white prisms (3.0 g, 88%), m.p. 117–120°. Since they decomposed very rapidly indeed they were characterized indirectly as described below.

N-(*4-Carbomethoxy-2,6-dinitrophenyl*)*pyridinium 4'-Carbomethoxy-2',6'-dinitrophenoxide* (I*b*)

(*a*) The pyridinium chloride I*a* (3.4 g) was dissolved in water (10 ml) and shaken with silver oxide (freshly prepared from 3.4 g of silver nitrate). Filtered from the silver compounds, the solution was slowly added to a suspension of methyl 3,5-dinitro-4-hydroxybenzoate (II*a*) (27) (2.5 g) in boiling water (150 ml). The bright yellow precipitate was recovered, washed with water, and then with acetone (100 ml) to remove unchanged phenol. The initial melting point of 236–237° (decomp.) was raised to 242–243° (k) (decomp.) by two recrystallizations from acetone. Found: C, 46.67, 46.52; H, 2.72, 2.77%. Calc. for $C_{21}H_{15}O_{13}N_5$: C, 46.25; H, 2.77; N, 12.84%.

(*b*) The yellow needles, m.p. 240–242° (uncorr.), obtained as a by-product in the preparation of IV*a* as described above were the same substance as that obtained in (*a*) part (mixture melting point, identical infrared spectra). Found: C, 47.90; H, 2.89; N, 12.88%. The presence of the activated N-phenylpyridinium group was shown by the slow solubility of the crystals in cold dilute potassium hydroxide to give a deep red coloration (20)—a test not given by the diphenyl ethers or dinitrohydroxybenzoic acids of this series. When this preparation of the quaternary salt (0.35 g) was heated for 3 hours on the steam bath with dry pyridine (3 ml) and the mixture poured onto ice, the solid recovered and recrystallized from acetone, unchanged quaternary salt was obtained in a yield of 0.2 g, m.p. 240–242° (uncorr.). Thus the salt is resistant to hydrolysis and to transformation into a diphenyl ether (19).

(*c*) The yellow needles, m.p. 241–242°, isolated from the preparation of VI*a* as above were also identical with those from (*a*) and (*b*) (mixture melting point, infrared spectra). Another sample of the yellow needles from the same source was recrystallized four times from acetonitrile and twice from acetone. Found: C, 46.18, 46.18; H, 2.30, 2.25; N, 12.98, 12.85%. Allowed to stand in the cold with dilute potassium hydroxide solution, the crystals slowly gave the deep red color characteristic of activated N-phenylpyridinium compounds.

Further proof of identity and structure is given in the next section.

Decomposition of the Quaternary Salt I*b*

(*a*) A sample of the quaternary salt I*b* (3.0 g, prepared as in "*a*" above) was stirred 5 minutes with dilute hydrochloric acid. The deep yellow color of the phenoxide was slowly replaced by the cream color of the insoluble decomposition product. This precipitate on recovery was shown to be methyl 3,5-dinitro-4-hydroxybenzoate (II*a*) by melting point and mixture melting point—a demonstration of the anion of the quaternary salt.

The aqueous filtrates after being neutralized with sodium bicarbonate gradually deposited a yellow solid which was recovered next morning, yield 0.88 g. Four recrystallizations from acetone converted it to long pale yellow needles, m.p. 244–245° (uncorr.) (decomp.).

(*b*) A sample of I*b*, recovered from the preparation of IV*a*, and as described in part (*b*) of the previous section, gave the same results. In particular, the precipitate from the neutralized solution had the same infrared spectrum as that described in part (*a*) of this section. Thus the identity of the two specimens of I*b* had been demonstrated.

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