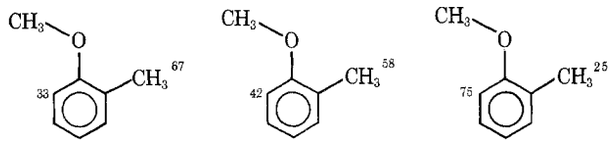
Interesting product distribution shifts were observed in the above metalations of **2** with *n*-butyllithium, *tert*-butyllithium, and *n*-butyllithium–TMEDA as indicated below.



n-BuLi *t*-BuLi *n*-BuLi–TMEDA

The numbers indicate the percentage of total metalation observed at each position. These results are also explainable in terms of the steric environment of the ortho hydrogens and the oligomer size of the alkyllithium reagent. The expected stable conformation of **2** would also be **6**.[12] Since *tert*-butyllithium is tetrameric[10] in hydrocarbon, the oligomer size of the metalation reagents would be expected to decrease in the order *n*-BuLi > *t*-BuLi > *n*-BuLi–TMEDA. The product distributions observed in these metalation reactions of **2** are consistent with the concept of the alkyllithium reagent with the least steric requirement effecting the largest amount of metalation at the hindered ortho position.

These product distribution results may also be rationalized in terms of the base strength of the reagents, which increases in the order *n*-BuLi < *t*-BuLi < *n*-BuLi–TMEDA.[8,13] A correlation is observed which indicates that the ratio of ring to lateral metalation increases with the base strength of the metalation reagent. The same conclusion was reached by Broaddus[5] concerning the metalation of toluene with *n*-butyllithium–TMEDA. He believed that the metalation reaction was controlled by proton abstraction processes and compared his data to the results of base-catalyzed isotopic exchange reactions of toluene. These results revealed a decreasing reactivity of benzylic positions relative to ring positions with increasing base strength. Broaddus rationalized his results in terms of the principle[14] that the C–H bond will be broken to the largest extent in the transition state involving the weakest base. Therefore, it may be reasonably proposed that electron delocalization stabilizing factors will also be largest with the weakest base. When more charge is developed on carbon, delocalization is a more important factor and thus reaction is favored at benzylic positions relative to ring positions.[5]

In any case the degree of complexation of the alkyllithium reagent with the oxygen of **2** does not appear to be the predominant factor in determining the yield or position of metalation. This argument seems even clearer for the metalations of anisole[2] and **1**[1] in ether solvent, where the coordination between *n*-butyllithium and the anisole substrates would be negligible based on the cited nmr data.[6,7]

Experimental Section

A. General Considerations. Solutions of *n*-BuLi in cyclohexane and *t*-BuLi in pentane were obtained from Foote Mineral Co. The concentration of the organolithium reagents used was determined by the method of Gilman and Cartledge.[15] Cyclohexane was refluxed for several hours over lithium aluminum hydride, distilled, and stored over freshly cut sodium. TMEDA (Aldrich Chemical Co.) was distilled from $LiAlH_4$ and stored over Linde MS-4A molecular sieve. *o*-Cresol was obtained from Eastman Chemical Co. and used without further purification.

B. Metalation of *o*-Methylanisole. *o*-Methylanisole was prepared from *o*-cresol with sodium hydroxide and dimethyl sulfate using the standard procedure.[16] Following fractional distillation *in vacuo* no impurities were detected by gc analysis and an nmr spectrum was consistent with expectation.

The general apparatus and procedure for the metalation reactions, carbonation, and conversion of the products to their methyl esters has been previously described.[9] The product methyl esters were analyzed on a Varian Aerograph 711 using an FFAP column at 210° and a carrier gas flow rate of 400 cc/min. All of the chromatograms exhibited two peaks with retention times of 22.3 and 29.1 min which varied in size according to the reaction conditions. The components responsible for these peaks were isolated by preparative scale gc and identified by their nmr spectra. The nmr spectrum of the component with the retention time of 22.3 min showed a singlet of three protons at δ 2.28, a singlet of three protons at δ 3.77, a singlet of three protons at δ 3.84, and a complex multiplet of three protons at δ 6.74–7.65. This spectrum is clearly representative of methyl 2-methoxy-3-methylbenzoate, the product of metalation ortho to the methoxy group. The nmr spectrum of the component appearing at 29.1 min exhibited a singlet of two protons at δ 3.54, a singlet of three protons at δ 3.62, a singlet of three protons at δ 3.79, and a complex multiplet of four protons at δ 6.62–7.36. This spectrum is interpretable only for methyl *o*-methoxyphenylacetate, the product of metalation of the methyl group.

The product composition of these reactions was determined by the relative peak areas of the chromatograms as measured by a Disc integrator.

Registry No.—**2**, 578-58-5; **3** methyl ester, 52239-62-0; **4** methyl ester, 27798-60-3.

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2,6-Dinitro-*N*-(2-imidazolyl)-*p*-toluidine

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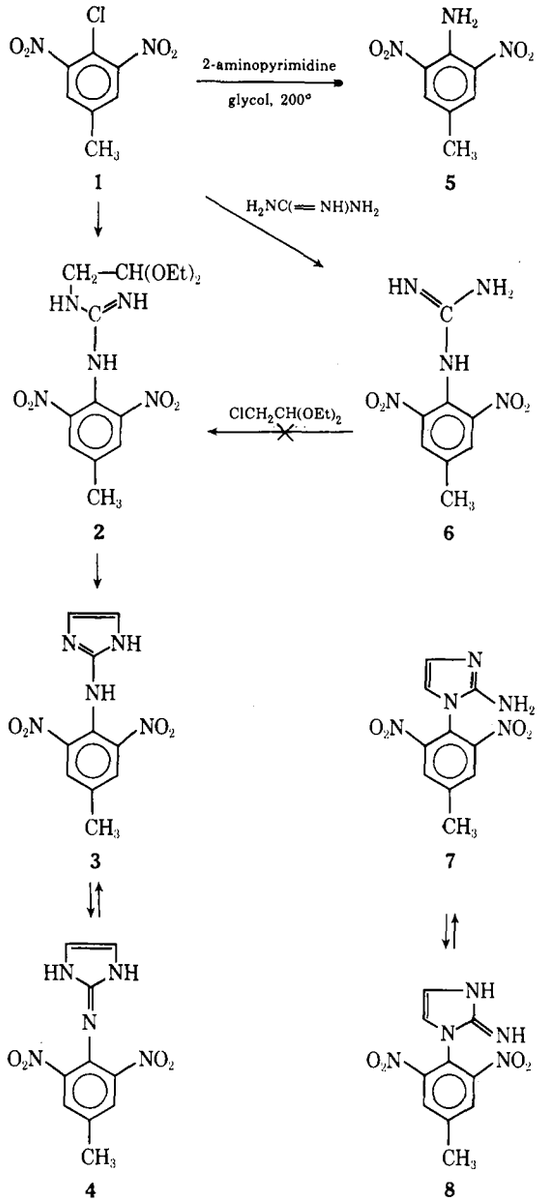
During the course of other work it became necessary to prepare 2,6-dinitro-*N*-(2-imidazolyl)-*p*-toluidine (**3**) for biological screening. This preparation could not be achieved by the direct displacement of chloride ion from 4-chloro-3,5-dinitrotoluene (**1**) by 2-aminoimidazole. Although such a displacement by aliphatic and aromatic amines[1,2] as well as alkoxide ions[3] is well known, our initial few attempts to condense **1** with 2-aminoimidazole, and another more stable heterocyclic amine, were not successful. For example, heating **1** with 2-aminoimidazole in dimethylformamide at 135° for 7 hr gave an intractable mixture of at least four major components. On the other hand, when the same reactants were heated under reflux in ethanol for 8 hr, nearly all **1** was recovered unchanged. Treating **1** with 2-aminopyrimidine (1:2 molar ratio) in glycol at 135° for 24 hr resulted in little change. Unexpectedly, at higher temperatures **1** reacted completely to afford 2,6-dinitro-*p*-toluidine (**1** → **5**) and a substantial amount of tar. A possible

course of this reaction was subsequently traced to an attack of glycol on 2-aminopyrimidine accompanied by evolution of ammonia. The latter reacted with 1 to give 5. The reaction of 1 with heterocyclic amines was not investigated further. A second route toward 3 (1 → 6 → 2 → 3) was also abandoned because 6 could not be converted to 2 by alkylation with chloroacetaldehyde diethyl acetal.



1 5 2 6 3 7 4 8

The synthesis of 3 was then achieved by building up the imidazole moiety in the following manner. Heating *N*-(2,2-diethoxyethyl) guanidine[4] with 1 in methanol gave 2 (61%) along with a lesser amount of 3,5-dinitro-4-methoxytoluene from the reaction of 1 with the solvent. The nmr spectrum of 2 was in accord with the assigned structure. The signals for the adjacent CH_2 and NH protons appeared as triplets at 3.28 and 6.16 ppm, respectively, while those of the other two NH protons formed a sharp singlet at 5.78 ppm. Upon deuteration all NH peaks exchanged, and the methylene triplet collapsed into a doublet, establishing firmly the NH positions and those of the aliphatic portion of the molecule.

Ring closure of 2 was carried out in concentrated hydrochloric acid[5] to yield a yellow substance which, conceivably, could be one of two products from two different reaction paths. According to one of the possible paths, the aldehyde moiety generated through acidic hydrolysis condenses with the imino group of 2 to give 3. Alternatively, condensation with the secondary aromatic NH leads to the isomeric structure 7. In addition, structures 3 and 7 could exist in the form of their tautomeric counterparts 4 and 8. Ir spectra did not permit an unambiguous distinction among the four possible structures. Thus, dilute solutions of the condensation product in chloroform showed two peaks of medium intensity at 3430 and 3250 cm^{-1}, respectively. These could be attributed to the ν_{as} and ν_s modes of the primary amine group of 7 or the two secondary ν(NH) vibrations of the imidazole[6] and amino groups of 3. Intramolecular hydrogen bondings between NH and NO_2 and the imidazole ring polymers[6] were also evident because the lower frequency band was rather broad with shoulders. Structures 4 and 8 are not consistent with the absorption at 3430 cm^{-1}, since they possess only secondary NH groups and are devoid of the imidazole aromatic ring. Convincing evidence against 7 and 8 and in support of 3 was provided by the nmr spectrum of the cyclization product, which in addition to the methyl frequency at 2.4 ppm exhibited only two very sharp signals in the aromatic region. The signal at 8.1 ppm was assigned to the phenyl protons in agreement with the same signals at 7.88 and 7.84 ppm for 2 and 6, respectively. The second sharp signal at 6.67 ppm is in accord with the magnetic equivalency[7] of the two CH protons of the imidazole ring of 3. Although the peaks for the two NH protons of 3 were too broad to be detected,[8] deuteration confirmed the presence of the two exchangeable hydrogens. Structures 7 and 8 were excluded on the basis that their imidazole CH protons are nonequivalent and should exhibit two signals[9] instead of the observed one. Consequently, structure 3 was assigned to the ring closure product.

Finally, evidence against a completely planar 3 was found in the uv–visible spectra of 2, 3, 5, and 6, which showed that considerable changes of the higher wavelength absorption occurred. Compound 5 absorbed at 438 nm, whereas 2 and 6 absorbed at 349 and 343 nm for a hypsochromic shift of 89 and 85 nm, respectively. The ϵ value also decreased by approximately 70%, from 7300 for 5 to 2400 for 2. These significant changes of λ_{max} and ϵ in going from an amino to a guanidino group are indicative of the substantial decrease in overlap between the phenyl π electrons and the lone pair of the nitrogen atom adjacent to it. The "freeze" of this nitrogen electron pair should be due to its engagement into resonance within the quanidino moiety, which is opposed to the resonance with the phenyl ring. With the formation of the imidazole ring (3), the resonance within the guanidino group is suppressed, since two of its nitrogen atoms now participate in the resonance of the imidazole ring. Actually, the two rings and the connecting nitrogen should be expected to interact[2] and compound 3 should absorb at a wavelength higher than 438 nm. The fact that 3 absorbed at 411 nm can be attributed to steric hindrance which forces the two rings at an angle with respect to each other. In a similar structure, *N*-picryl-*p*-iodoaniline for example, the two aryl groups have been reported[10] to be tilted by 65° relative to each other.

Experimental Section[11]

***N*-(2,2-Diethoxyethyl)guanidine Sulfate.** The compound was prepared as described previously[4] in 80% yield, mp 154–156° (lit.[4] mp 148–152°).

***N*-(2,2-Diethoxyethyl)-*N'*-(2,6-dinitro-4-methylphenyl)-guanidine (2).** To a solution of sodium hydroxide (2 g, 0.05 mol) in methanol (200 ml), *N*-(2,2-diethoxyethyl)guanidine sulfate (12.3 g, 0.0275 mol) was added and the mixture was stirred for 30 min. After the addition of 3,5-dinitro-4-chlorotoluene (1, 5.4 g, 0.025 mol) the reaction mixture was refluxed for 28 hr and filtered, and the filtrate was evaporated to dryness under vacuum to yield an oily residue. The residue was triturated with water (three 30-ml

portions) and crystallized from ethanol to give crude **2** (4 g), which was purified by four recrystallizations from benzene: yellow crystals, mp 139–140°; yield 1.6 g (18%); nmr (DMF-d_6) δ 1.15 (t, 6, OCH_2CH_3), 2.38 (s, 3, aromatic CH_3), 3.28 (t, 2, $HNCH_2CH$), 3.6 (m, 4, OCH_2CH_3), 4.65 (t, 1, $HNCH_2CH$), 5.78 (s, 2, $-C(=NH)NH-$), 6.16 (t, 1, $NHCH_2CH$), 7.88 (s, 2, aromatic H); λ_{max} (MeOH) 218 nm (ϵ 21,000), ~240 sh (15,000), 349 (2400).

Anal. Calcd for $C_{14}H_{21}N_5O_6$: C, 47.32; H, 5.96; N, 19.71; O, 27.01. Found: C, 47.12; H. 5.95; N, 19.69; O, 27.14.

The filtrates from the ethanol and benzene crystallizations were combined and evaporated to dryness under vacuum to yield a gummy residue (7 g) which was dissolved in benzene and chromatographed on alumina. Elutions with benzene gave 1.2 g of 3,5-dinitro-4-methoxytoluene, mp 121–123° (lit.[3] mp 123–124°). Further elutions with benzene and benzene–chloroform solutions of increased polarity yielded additional pure **2** (3.8 g, mp 139–140°). Total yield was 5.4 g (61%).

2,6-Dinitro-*N*-(2-imidazolyl)-*p*-toluidine (3). Intermediate **2** (1.4 g, 4 mmol) in concentrated hydrochloric acid (6.5 ml) was heated on a steam bath for 1 hr. The reaction mixture was diluted with water (25 ml), boiled to remove hydrochloric acid, decolorized with charcoal, cooled, and neutralized with ammonium hydroxide. The precipitated red crude **3** was purified by crystallization from ethanol (mp 219–221°, yield 0.4 g, 39%). An additional recrystallization from ethanol gave pure **3**: mp 220–221.5°; nmr (DMF-d_6) δ 2.4 (s, 3, CH_3), 6.67 (s, 2, imidazole H), 8.1 (s, 2, aromatic H); λ_{max} (MeOH) 241 nm (ϵ 17,500), 411 (4000).

Anal. Calcd for $C_{10}H_9N_5O_4$: C, 45.63; H, 3.45; N, 26.61; O, 24.31. Found: C, 45.61; H, 3.45; N, 26.40; O, 24.08.

3,5-Dinitro-4-guanidinotoluene (6). Guanidine hydrochloride (4.8 g, 0.05 mol) was added to a solution of sodium hydroxide (2 g, 0.05 mol) in methanol (50 ml) at 10–12°. The mixture was stirred for 5 min, the precipitated sodium chloride was filtered off, and the methanolic guanidine so obtained was added to a solution of **1** (5.4 g, 0.025 mol) in methanol (150 ml). The reaction mixture was refluxed for 20 hr, cooled, clarified by gravity filtration, and evaporated to dryness under vacuum to give a semisolid dark residue. The residue was stirred in water (100 ml) for 15 min, filtered off, and recrystallized from acetone–methanol. The crude product obtained was refluxed in benzene (100 ml) for 1 hr, filtered off, and recrystallized from methanol to give pure **5**: mp 235–236°; yield 1.1 g (18%); nmr (DMF-d_6) δ 2.37 (s, 3, CH_3), 5.84 (s, 4, $NHC(=NH)NH_2$), 7.84 (s, 2, aromatic H); λ_{max} (MeOH) 216 nm (ϵ 19,000), ~240 sh (~ 15,000), 343 (2500).

Anal. Calcd for $C_8H_9N_5O_4$: C, 40.17; H, 3.79; N, 29.28. Found: C, 40.08; H, 3.84; N, 29.47.

The aforementioned benzene solution was concentrated and cooled to yield 3,5-dinitro-4-methoxytoluene (2.1 g) formed by the concurrent reaction of **1** with the solvent methanol, mp 123° (lit.[3] mp 123–124°).

Reaction of 4-Chloro-3,5-dinitrotoluene with 2-Aminopyrimidine. 2,6-Dinitro-*p*-toluidine (5). A solution of **1** (54.2 g, 0.25 mol) and 2-aminopyrimidine (52.3 g, 0.55 mol) in glycol (125 ml) was stirred at 195–200° for 3 hr, cooled, and filtered. The black solid obtained was dissolved in acetone (500 ml) and filtered from undissolved tar, and the filtrate was brought to dryness under vacuum to yield an orange solid. This solid was purified by crystallization from methylene chloride–ethanol, mp 167–171°, yield 19.4 g (39%). Two additional recrystallizations from chloroform–methanol and benzene gave pure **5**, mp 170–171° (lit.[12] mp 172°). The compound was identified by ir spectrum and mixture melting point with an authentic sample: λ_{max} (MeOH) 224 nm (ϵ 16,000), 252 (7300), 438 (7300).

Anal. Calcd for $C_7H_7N_3O_4$: N, 21.31. Found: N, 21.58.

Registry No.—**1**, 5264-65-3; **2**, 52225-72-6; **3**, 52225-71-5; **5**, 6393-42-6; **6**, 52322-50-6; *N*-(2,2-diethoxyethyl)guanidine sulfate, 52225-73-7; guanidine hydrochloride, 50-01-1; 2-aminopyrimidine, 109-12-6.

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Preparation of *cis*-Methyl α-(Tetrahydro-2-furylidene)acetate

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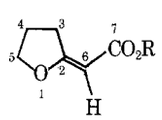
Several methods for the preparation of *trans*-α-(tetrahydro-2-furylidene)acetates **1** have been reported in the literature.[1,2] We wish now to report the successful preparation of the thermodynamically less stable *cis*-methyl α-(tetrahydro-2-furylidene)acetate (**2**) by stereospecific displace-



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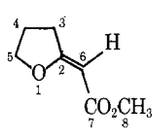
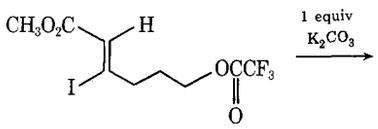


2

ment of iodide ion in *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate (**4**).

trans-Methyl 3-iodo-6-hydroxy-2-hexenoate (**4**) was obtained by hydrolysis of *trans*-methyl 3-iodo-6-trifluoroacetoxy-2-hexenoate (**3**)[3] with 1 equiv of potassium carbonate in water–methanol–THF (10:1:2). Treatment of **4** with sil-



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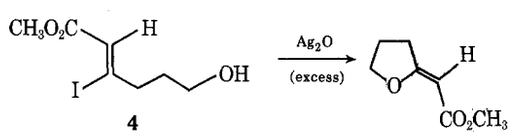

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2

ver oxide (excess) in ethyl ether gave a 1:1 mixture of the cis isomer **2** and the starting alcohol which could be separated by rapid partial distillation at reduced pressure. However, slow distillation at reduced pressure converts the cis isomer quantitatively into the trans isomer (**1**).[4] At room temperature the cis isomer slowly (several days) isomerizes to **1**. This latter isomerization (**2** to **1**) limited the reaction time that could be used for the conversion of iodide **4** to furylidene **2**. The cis isomer (**2**) could be stored for up to 4 months at −10° without detectable changes in structure.

Under more vigorous cyclization conditions the iodo alcohol **4** could be completely converted to a furylidene structure; however, the products thus formed were mixtures of geometric isomers. For example, treatment of **4**