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STERIC RETARDATION IN ACTIVATED NUCLEOPHILIC AROMATIC SUBSTITUTION. THE REACTIONS OF FLUORO-4-NITROBENZENE WITH SOME METHYL-SUBSTITUTED PIPERIDINES IN DIMETHYL SULFOXIDE.

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Recently Suhr has reported (1) that the relative rates for the reactions of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine and cis-2,6-dimethylpiperidine* at 25°C in dimethyl sulfoxide (DMSO) are 30, 1.5 and 1, respectively.

Much greater steric retardations have been observed in the 2,4-dinitro series in benzene. In fact, we have shown that the relative rates for the reactions of chloro-2,4-dinitrobenzene with piperidine, 2-methylpiperidine, trans-2,6-dimethylpiperidine and cis-2,6-dimethylpiperidine in benzene at 25°C are 214000, 101, 1, and 0.16, respectively (2). For the reactions of fluoro-2,4-dinitrobenzene with the first three amines the relative – uncatalyzed – rates are 59700, 228, and 1 (2).

The lesser susceptibility to steric effects exhibited by the p-nitro series could either be a consequence of the lack

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* In the original paper (1) the amine is simply named 2,6-dimethylpiperidine. However, the boiling point reported, 128°C, is characteristic of the cis isomer [see ref. cited in (2)].

of the o-nitro group or (and) of the use of a solvent, DMSO, which has been reported (3) to be some thousand-fold ''faster'' than benzene in reactions of this kind. With the aim to assess the weight of these two factors we started a new investigation of these reactions.

In the course of this research it has been discovered, however, that some of the aforementioned data for the p-nitro series are in error. Thus we report here some new data for this series. Rate data for the reactions of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine and *trans*-2,6-dimethylpiperidine in DMSO are collected in Table I. Comparison of these results with those reported by Suhr (1) shows that:

a) Our and Suhr's rates for the reaction of piperidine agree within 12%.

b) Our rate for the reaction of 2-methylpiperidine[*] is one order of magnitude lower than that reported by Suhr (1).

c) Our rate for the reaction of *trans*-2,6-dimethylpiperidine[**] is two orders of magnitude lower than that assigned by Suhr (1) to the reaction of the *cis* isomer. As the latter is known to be less reactive than the *trans* isomer in reactions of this kind (2) – which is quite easily understandable on stereochemical grounds – the rate reported for the reaction of the

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[*] Formation of N-4-nitrophenyl-2-methylpiperidine (sublimed, melts at 61.5 - 62.5°C, uncorrected, when rapidly heated). *Anal*. Calcd. for $C_{12}H_{12}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.5; H, 7.5; N, 12.6. The structure is consistent with the PMR spectrum.

[**] Formation of N-4-nitrophenyl-*trans*-2,6-dimethylpiperidine, m.p. 95-96.5°, uncorrected, is quantitative. The PMR spectrum is in agreement with this structure.

TABLE I

Second-order rate coefficients, $\underline{k}$, for the reaction of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine and trans-2,6-dimethylpiperidine in dimethyl sulfoxide.[*]

Piperidine $\underline{M}$ x 10	ArF $\underline{M}$ x 10^3	temp. °C	10^5 x $\underline{k}$ mole^{-1} l. sec.$^{-1}$
0.208	10.7	25.2	1010[a]
2-methyl-piperidine[**] $\underline{M}$ x 10			
5.05	50.0	25.2	1.82
7.76	52.7	25.2	1.70[a]
trans-2,6-dimethyl-piperidine[***] $\underline{M}$ x 10			
1.41	9.85	75	1.03
6.95	49.6	75	1.01
1.41	9.85	100	3.24
6.95	49.6	100	3.05

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[*] Dimethyl sulfoxide was fractionated and then redistilled over barium oxide. For the experiments labelled with a the solvent was further distilled over calcium hydride.

[**] Good kinetic plots where obtained up to 90% reaction completion in this and in all other kinetic experiments reported in this communication.

[***] These experiments were carried out under nitrogen.

cis amine (1) must be erroneous by more than two orders of magnitude.*

The second-order rate coefficient for the reaction of trans-2,6-dimethylpiperidine extrapolated to 25°C from the data of Table I is 7×10^{-7} mole^{-1} l. sec.^{-1}. Thus the relative rates for the reactions of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine, and trans-2,6-dimethylpiperidine in DMSO at 25°C are 13500, 26, and 1, respectively. The comparison of these results with those mentioned previously for the analogous reactions of fluoro-2,4-dinitrobenzene in benzene shows that the pattern of the relative rates found in the p-nitro series is not drastically changed by the introduction of one o-nitro group. If the relative rates in any of these two reaction series are not strongly affected by the change of solvent from benzene to DMSO –

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* We have carried out some experiments also with cis-2,6-dimethylpiperidine. In a typical run, a DMSO solution of fluoro-4-nitrobenzene 0.1 M and amine 1.2 M was let at 100°C for two days in a sealed tube under nitrogen. From the reaction mixture the only product likely to be N-4-nitrophenyl-cis-2,6-dimethylpiperidine was isolated in a 10% yield by preparative layer chromatography as yellow crystals m.p. 147-149°C, uncorrected. Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.7; H, 7.7; N, 12.0. Found: C, 67.1; H, 7.7; N, 11.9. The PMR spectrum at 60 Mc of a 10% solution in $CDCl_3$ with tetramethylsilane as internal standard shows an aromatic AA'XX' system, a broad absorption (2 protons) centered at δ=4.21 p.p.m. which could be attributed to the methine protons, a sharp peak at δ=1.81 p.p.m. (6 protons), and a doublet centered at δ=1.25 p.p.m., J=6.3 cps, (6 protons), which could be ascribed to the methyl protons. The absorption in the methylene region is so remarkably sharp, however, that we prefer to do additional experiments before definitely assign the structure. The oily material reported by Suhr for this case (1) is likely to have arised mainly from the reaction of fluoro-4-nitrobenzene with very reactive amines present as impurities in the sample of cis-2,6-dimethylpiperidine used.

which indeed is not known at present — these results can be rationalized on the basis of the tetrahedral nature of the transition state. In such a model the o-nitro group can adapt itself between the entering and the leaving groups, thus attaining coplanarity with the benzene ring.

Full experimental details will be reported later on completion of this work.

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REFERENCES

(1) H. Suhr, Ann., 689, 109 (1965).
(2) F. Pietra and F. Del Cima, Tetrahedron Letters No. 18, 1925 (1966) and previous papers here referred to.
(3) H. Suhr, Chem. Ber., 97, 3277 (1964).