3.0 g. of osmium tetroxide in 30 cc. of ether was tightly stoppered and allowed to stand for 308 hours. After this time two types of solid were present in the reaction mixture, a fine, black adherent precipitate and a quantity of coarse granules, coated with the black material. Since the desired product is quite sparingly soluble in ether, the mixture was extracted and digested with benzene. The dark-colored benzene solution was washed free of osmium tetroxide with aqueous sodium thiosulfate; a very heavy emulsion which developed was separated by filtration through Darco. The benzene layer was then washed with water, dried with sodium sulfate and concentrated. Three crops of crystals were obtained from this solution, amounting to 550 mg. The first crop was recrystallized from ethyl acetate to give white needles, m. p. 208–210°; $[\alpha]^{26}D$ +31° (c 1.126 in chloroform).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.1; H, 8.8. Found: C, 69.3; H, 8.9.

The benzene-insoluble osmium residue from the reaction mixture was treated with 10 ml. of concd. nitric acid. The black solid became gummy, and copious red fumes were evolved. After 15 seconds, the mixture was treated with ice-water and extracted with benzene. The benzene solution was processed in the manner described above. The residue remaining after removal of the benzene was crystallized from ethyl acetate to give white crystals, wt. 80 mg., m. p. 189–191°; after several recrystallizations from this solvent, m. p. and mixed m. p. with first crop above 205–207°.

Summary

1. A new method for the preparation of 17-pregnen-21-ol compounds from the 17-pregnen-21-oic acids is reported. The 17-pregnen-21-ol compounds so obtained have been converted to the corresponding products containing the 17α,20β,-21-triol side chain.

2. A new synthesis of compounds containing the 17α,21-diol-20-one side chain from the corresponding 20-bromo-17-pregnen-21-oic acids has been described.

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RECEIVED APRIL 21, 1950

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Nucleophilic Displacement in the Naphthalene Series

BY ERNST BERLINER, MARGARET JOSEPHINE QUINN[1] AND PATRICIA JONES EDGERTON[1]

The greater reactivity of the α-position in naphthalene, predicted by modern theories, is well substantiated by substitution reactions, measurements of physical constants and quantum mechanical calculations.[2] The α-position should also be more reactive toward displacement reactions, but very little is known about nucleophilic displacements on the halonaphthalenes.[3] The present investigation was undertaken in order to see whether, under comparable conditions, the α-position is more reactive toward nucleophilic reagents than the β-position, as demanded by the theory and all available experimental evidence. While this work was in progress, Pullman, Rumpf and Kieffer[4] determined the rate of exchange of the bromonaphthalenes with radioactive lithium bromide. They found that in every case β-bromonaphthalene reacted faster than the α-isomer and attributed this to the greater amount of double bond character of the α-isomer.

TABLE I

THE REACTIONS OF HALONAPHTHALENES WITH PIPERIDINE

Naphthalene	k_{165} × 10^4, hours^{-1}	k_{200} × 10^4, hours^{-1}	E, kcal.		log PZ	
1-Iodo-	17.0	121	23.1	±0.95	8.76	±0.45
2-Iodo-	21.1	171	24.6		9.60	
1-Bromo-	8.56	70.9	24.9	±0.7	9.36	±0.35
2-Bromo-	14.9	156	27.6		10.95	
1-Chloro-	1.48					
2-Chloro-	1.86					
Iodobenzene	9.4	70	23.6	±1.0	8.75	±0.5
Bromobenzene	5.2					
Chlorobenzene	0.64					

In the present study the displacement reactions were carried out on α- and β-halonaphthalenes, 1-nitro-2-halo- and 2-nitro-1-halonaphthalenes with piperidine as the nucleophilic reagent and solvent. In Table I are recorded the results for the halonaphthalenes, which were studied at 165 and 200°; data on the halobenzenes are also included. In all cases the β rather than the α-isomer is the more reactive. The energies of activation and PZ factors indicate that the relative order of reactivity of the α- and β-isomers is not caused by a difference in activation energies, but by a difference in the PZ factors. This is particularly evident with the bromonaphthalenes. Although β-displacement proceeds with the greater energy of activation, the faster reaction occurs at the β-position because of a greater PZ factor. The halobenzenes, as expected, react invariably slower than the corresponding halonaphthalenes.

The reversal of the relative rates from those expected is perhaps somewhat misleading *because* of the high temperature at which the reactions had to be carried out. The E and PZ factors of the two reactions are such that relatively less β-substitution must occur as the temperature decreases and at some sufficiently low temperature the α-halonaphthalenes will be more reactive than the

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[1] Part of a thesis submitted to the Department of Chemistry of Bryn Mawr College in partial fulfillment of the requirements for the M.A. degree.

[2] Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 267; Ketelaar and van Oosterhout, *J. Chem. Phys.*, **13**, 448 (1945); *Rec. trav. chim.*, **65**, 448 (1946); see also ref. 4; Wheland and Pauling, THIS JOURNAL, **57**, 2086 (1935); Wheland, *ibid.*, **64**, 900 (1942); Daudel, *J. Chem. Phys.*, **16**, 639 (1948); Pullman, *Ann. chim.*, **2**, 5(1947).

[3] Petrenko-Kritschenko, *Ber.*, **62**, 581 (1929).

[4] Pullman, Rumpf and Kieffer, *J. chim. phys.*, **45**, 150 (1948).

corresponding β-compounds. The situation is like the one visualized by Dewar[5] for electrophilic substitution in naphthalene for which $E_\alpha < E_\beta$ and $PZ_\alpha < PZ_\beta$. In such cases k_β must increase more rapidly with increasing temperature than k_α, and a temperature is reached at which k_α and k_β are reversed.

The second set of data was obtained from halogenated naphthalenes in which the halogen was activated by an ortho nitro group. Because the nitro group might have a different influence depending on whether it is in the α- or β-position, this reaction is not strictly comparable to the high temperature reaction. The results are recorded in Table II.

TABLE II

THE REACTION OF HALONITRONAPHTHALENES WITH PIPERIDINE

Naphthalene	k_0, hours^{-1}	k_{25}, hours^{-1}	E, kcal. ± 0.3	log PZ ± 0.2	Reaction, % at 45°[a]
1-Iodo-2-nitro-	0.107	0.856	13.5	9.84	
2-Iodo-1-nitro-	0.00771	0.0757	14.8	9.74	
1-Bromo-2-nitro-	1.10	5.51	10.4	8.37	91
2-Bromo-1-nitro-	0.0914	0.613	12.3	8.81	65
1-Chloro-2-nitro-	.847	4.60	10.9	8.66	51
2-Chloro-1-nitro-	.0785	0.470	11.6	8.18	46

[a] Ref. 6.

McLeish and Campbell[6] have studied the same bromo- and chloronaphthalenes and have determined the per cent. reaction at 45°. Their data are included in the table but were not used in the calculation of E and PZ.

When an activating group is in the ortho position, the relative rates of α- and β-displacement are reversed. In every case the α- halo-isomer is appreciably more reactive than the β-isomer. In this series the relative order of reactivity *is* caused by differences in activation energies although the differences are not very large. It is doubtful that the greater reactivity of the α- halo-isomers has anything to do with the greater power of conjugation of the α-position. The most important resonance forms in the transition state will be the ones which have the negative charge on the nitro groups, and there are equal numbers of such forms for each isomer. The minor differences contributed by other structures are probably insignificant, but if they contribute anything, their contribution will work in favor of the α-isomer. The rather large difference in rates between the α- and β-isomers is best explained on the basis of steric inhibition of resonance of the nitro group in the α-position. If the nitro group is not co-planar with the naphthalene ring, because of interference with the peri hydrogen, the β-halogen will be less activated, and the rate will fall off accordingly.[7]

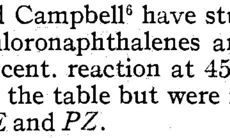

Fig. 1.

The reactions of the halonaphthalenes without the nitro group are presumably S_N2 displacements with a transition state analogous to that for S_N2 displacements in aliphatic halides.[8] The transition state is subject to steric hindrance in the α-position. Although reaction appears to be preferred electronically (and therefore energetically) in the α-position, the probability for reaction is greater in the unhindered β-position. Relations between the PZ factor and steric hindrance or the ortho effect have often been discussed and need not be repeated here.[9,10] If, however, in the reactions of the halonaphthalenes, displacement of the α-isomer is subject to steric hindrance the same might be expected to hold true for the reaction of the 1-halo-2-nitronaphthalenes. The halogen in the α-position, flanked by a nitro group, should be no less hindered, and still it reacts faster than its isomer. One possible explanation is that the two types of reaction proceed by slightly different reaction mechanisms. Whereas the high temperature reactions of the halonaphthalenes are one-step S_N2 displacements, the reaction of the halonitronaphthalenes is proposed to occur in two steps.[11] The first step leads to the formation of either a fairly stable intermediate or actually an intermediate compound. In either case this intermediate would represent a "valley" in the potential energy diagram. This intermediate, which is an anion, is pictured in Fig. 1.

Quinoid compounds of the above type, obtained from polynitro aromatic compounds and bases, have been isolated in several cases, and their presence is indicated by the color produced when polynitro compounds are treated with bases.[12] Their existence was convincingly demonstrated for the

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[5] Dewar, "Electronic Theory of Organic Reactions," Oxford University Press, Oxford, 1949, p. 174.

[6] McLeish and Campbell, *J. Chem. Soc.*, 1103 (1937).

[7] Probably for similar reasons the dipole moment of 1-nitro-2-naphthylamine is smaller than that of 2-nitro-1-naphthylamine. Vasil'ev and Syrkin, *Acta Physico. Chem. U. R. S. S.*, **9**, 203 (1938); *C. A.*, **33**, 7163 (1939).

[8] Hughes and Ingold, *J. chim. phys.*, **45**, 241 (1948); Hughes, *Trans. Faraday Soc.*, **37**, 627 (1941); Baker, *ibid.*, **37**, 635 (1941).

[9] See for instance: Remick, "Electronic Interpretations of Organic Reactions," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., pp. 217, 224; Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, Oxford, 1941, pp. 79, 250.

[10] The naphthalenesulfonyl chlorides offer an analogous case (Linetskaya and Sapozhnikowa, *Zhur. Prikl. Khim.*, **21**, 876 (1948); *C. A.*, **43**, 926 (1949)). The α-compound reacts slower than the β-isomer, in spite of a lower energy of activation. In the hydrolysis of naphthyl halides, however, Ingold and Patel (*J. Ind. Chem. Soc.*, **7**, 95 (1930)) found that the α-reacts faster than the β-isomer, probably because the S_N1 mechanism is not subject to as much steric hindrance as the S_N2 mechanism. See also Braun and Moldancke, *Ber.*, **56**, 2165 (1923), but these authors conducted the hydrolysis under heterogeneous conditions.

[11] See however Brady and Cropper (*J. Chem. Soc.*, 507 (1950)) who proposed an S_N2 type mechanism for the reaction of 1-chloro-2,4-dinitrobenzene with amines.

[12] Sidgwick, Taylor and Baker, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1942, pp. 259, 264, 265.

case of *m*-dinitrobenzene.[13] The nitrohalonaphthalenes develop an immediate yellow color when treated with piperidine, indicating a similar saltlike intermediate. The transition state for the formation of the intermediate has different spatial requirements from that of the high temperature reaction, because the approach of the piperidine is not accompanied by the recession of the halide. This may be sufficient to change the picture with regard to the *PZ* factors. The second step in the reaction is the breaking of the carbon halogen bond with a characteristic energy of activation of its own. The formation of the intermediate is probably a rapid process because of the favorable charge distribution created by the nitro group; the breaking of the carbon–halogen bond would then be the slow, rate determining step. The process of anionization of the halogens probably will not be very different energetically for the same halogen on either the α- or β-carbon, so that the total energy of activation and rate of reaction will ultimately depend on the ease of formation and the stability of the intermediate.

A further indication of a difference in reaction mechanism for the two reactions is the different order of reactivity of the halogens themselves. When the nitro group is absent, the observed order of reactivity of the halogens is $I > Br > Cl$. As far as could be ascertained from the literature this is invariably the case when halogenated benzenes are subjected to nucleophilic displacements.[14,15] This is also the order of reactivity of alkyl halides in S_N2 reactions.[16] With the nitro group in the ortho position the reactivity of the halogens is $Br > Cl > I$. Again, it is generally the case in *o*- and *p*-nitrohalobenzenes that the iodine is displaced less readily than bromine or chlorine (the latter two often reverse themselves).[17] No quantitative comparison with fluoronitro compounds is available, but from the published observations one would conclude that fluorine, when activated by a nitro group, is very easily removed,[18] so that the usual order of displacement is $(F >)\ Cl,\ Br > I$, or essentially the reverse of the order of displacement when the nitro group is absent. The order of reactivity of the halogens in the nitro activated reactions finds some parallel in their electronegativities, and this would be expected if the rate determining step is the anionization of the halogens. If the rate determining step is not the breaking away of the halogen, but the formation of the intermediate, the halogens must be specifically concerned with this process. They may work against the approach of the reagent and offer it greater resistance as their size becomes larger. If this were the only effect, it would account for the low reactivity of the iodo compounds.

Experimental

Materials.—The halogenated benzenes and naphthalenes were the best commercial grade samples and were redistilled *in vacuo* or recrystallized before use. 2-Iodonaphthalene (m. p. 54–54.6°) was prepared in 60–70% yield by an adapation of the method of Hodgson and Walker,[19] but the 1-isomer could not be made by this method.

The halonitronaphthalenes were all prepared from the corresponding nitroamines[20] by the method of Hodgson and Walker.[19] The 1-chloro-2-nitronaphthalene required a substantial excess of cuprous chloride. The melting points of the six compounds were: 1-chloro-2-nitro, 80.4–80.9°; 2-chloro-1-nitro, 98.8–99.8°; 1-bromo-2-nitro, 98–99°; 2-bromo-1-nitro, 103.6–104.6°; 1-iodo-2-nitro, 107–108°; 2-iodo-1-nitro, 89.7–90.5°. Monsanto piperidine, containing about 1% of pyridine and 1% of water, was used. Material that had been dried carefully and fractionated gave the same results.

Method.—High temperature reactions: Approximately 0.002–0.0025 mole of the halogen compound was weighed in a drawn-out pyrex test-tube; 4 ml. of piperidine was added, and the test-tube was sealed off. The thermostat, filled with hydrogenated vegetable oil (Spry), contained a heating unit inside the wall and was also heated in the bath with a knife heater. The bath was stirred with two stirrers, and the tubes, usually twelve for one run, were suspended in the thermostat by means of a wire basket. The temperature remained constant within ±1°. For analysis the contents of the test-tube were treated with water, and the organic material was extracted with benzene. The benzene extract was washed thoroughly with water, and the halide ion in the combined aqueous solutions was determined by the Volhard method. The results of two typical determinations follow.

Reaction with 4 ml. of piperidine at 165°

2-bromonaphthalene			2-iodonaphthalene		
Time, hr.	Reacn., %	$k \times 10^4$, hours^{-1}	Time, hr.	Reacn., %	$k \times 10^4$, hours^{-1}
24	3.58	15.2	24	4.89	20.9
24	3.55	15.1	24	4.99	21.3
48	6.63	14.3	48	10.25	22.5
48	6.65	14.3	48	10.22	22.5
24	3.66	15.5	60	11.59	20.5
24	3.62	15.4	60	11.27	19.9
48	6.83	14.7	26	5.32	21.0
48	6.84	14.8	26	5.42	21.4
	Av.	14.9	48	9.17	20.0
			48	9.44	20.7
				Av.	21.1

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(13) Farr, Bard and Wheland, This Journal, **71**, 2013 (1949). See also Canbäck, *Acta Chem. Scand.*, **3**, 946 (1949).

(14) Fluoro compounds react slower still than chloro compounds.

(15) Löwenherz, *Z. phys. Chem.*, **29**, 401 (1899); Lellmann and Geller, *Ber.*, **21**, 2279 (1888); Tronov, *J. Russ. Phys. Chem. Soc.*, **58**, 1278 (1926) [*C. A.*, **22**, 2737 (1928)]; Tronov and Krueger, *ibid.*, **58**, 1270 (1926) [*C. A.*, **21**, 3887 (1927)]; Krueger and Bednova, *J. Gen. Chem.* (*U. S. S. R.*), **3**, 67 (1933) [*C. A.*, **28**, 1593 (1934)]. However in the reaction of aryl halides and potassium amide in liquid ammonia at −33° the order of reactivity is $Br > I > Cl > F$; Bergstrom, Wright, Chandler and Gilkey, *J. Org. Chem.*, **1**, 170 (1936); Bergstrom and Horning, *ibid.*, **11**, 334 (1946).

(16) Hughes in "Reaction Kinetics," A General Discussion of the Faraday Society, 1937, pp. 194–195, and other references cited.

(17) Franzen and Bockhacker, *Ber.*, **53**, 1174 (1920); Rheinlander, *J. Chem. Soc.*, **123**, 3099 (1923); Sandin and Liskear, This Journal, **57**, 1304 (1935); Brewer and Turner, *J. Chem. Soc.*, 332 (1928) found that the order of displacement of the *p*-nitrohalobenzenes was $Br > I > Cl$, whereas for the ortho nitro and 2,4-dinitrohalides the orders were as given above, with the iodo compound the slowest.

(18) Rouche, *Bull. sci. acad. roy. Belg.*, 537 (1921) [*C. A.*, **17**, 2876 (1923)]; Gottlieb, This Journal, **58**, 532 (1936); Rarick, Brewster and Dains, *ibid.*, **55**, 1289 (1933); Holleman and Beekmann, *Rec. trav. chim.*, **23**, 249 (1904); Swartz, *ibid.*, **35**, 147 (1915).

(19) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(20) Lellmann and Remy, *Ber.*, **19**, 797 (1886); Hodgson and Walker, *J. Chem. Soc.*, 1205 (1933); Hartman and Smith, "Org. Syntheses," Coll. Vol. II, 1943, p. 438.

The average deviation of all values of the high temperature reactions from the recorded values was 4%. Reactions with the iodonaphthalenes were also conducted at 150°, but only a few runs were made and the results were not included in the calculation of the activation energies. At 150° the rate constant for the reaction of α-iodonaphthalene is 7.1 × 10^{-4} and for β-iodonaphthalene 8.7 × 10^{-4}. The per cent. reaction for the chloronaphthalenes and chlorobenzene at 165° and 48 hours was below 1%, but the values were reproducible. At 200° and 24 hours the per cent. reaction was between 25 and 35%. The reaction rates fell off somewhat in runs longer than 24 hours, probably because of some decomposition of the organic material, but since the results were calculated for runs which were conducted under similar conditions, the average rate constants are comparable. If only runs at 24 hours were compared, the relative order of the activation energies was the same, but the average error was smaller.

The low temperature reactions were conducted in 5-ml. volumetric flasks, the whole content of the flask being used for any one determination. The amounts of reagents and method of analysis were the same as those described above, except that piperidine (4 ml.) was brought to the desired temperature in the thermostat (±0.05°) before mixing the reagents. The 0° runs were conducted in a large, covered dewar flask filled with ice and water. The average deviation of all runs from the chosen values was 1.9%. Some typical data are

Reaction between 1-chloro-2-nitronaphthalene and piperidine (4 ml.) at 25°

Time, min.	Concn. 1-chloro-2-nitronaphthalene × 10^3	Reaction, %	k × hours^{-1}
10	2.430	53.97	4.66
15	2.415	68.08	4.57
20	2.333	77.91	4.53
25	2.362	84.96	4.55
30	2.335	90.32	4.67
		Av.	4.60

First order rate constants were calculated in the usual way. The energies of activation were calculated from the equation $\ln k_2/k_1 = E(T_2 - T_1)/RT_1T_2$, and the PZ factors from the equation $\ln k = \ln PZ - E/RT$.

Acknowledgment.—Part of this work was aided by a Frederick Gardner Cottrell Grant of the Research Corporation, for which we express our thanks.

Summary

1. The rate of displacement of the halogen from α- and β-halonaphthalenes and 1-halo-2-nitro- and 1-nitro-2-halonaphthalenes with piperidine was determined at several temperatures.

2. In the temperature range 165–200° the β-halonaphthalenes react faster than the α-isomers. Between 0 and 25° the 1-halo-2-nitronaphthalenes react faster than the 2-halo-1-nitronaphthalenes.

3. Possible reasons for the observed order of reactivity are discussed.

BRYN MAWR, PA. RECEIVED MARCH 17, 1950

NOTES

Substituted Isobutyrophenones

BY RODERICK A. BARNES[1] AND LOUIS GORDON

The preparation of alkyl–aryl ketones having a methoxyl group on the aromatic ring may be effected either by the Fries rearrangement[2] followed by methylation or by a Friedel–Crafts reaction with the methyl ether of a phenol.[3] Two isobutyrophenones having both halogen and methoxyl substituents were of interest in connection with a projected synthesis. The observations concerning the application of the two preparative methods may be of interest for related alkyl-aryl ketones.

The Fries rearrangement of *p*-chlorophenyl isobutyrate was previously reported by von Auwers, Baum and Lorenz.[4] When this ester was heated with aluminum chloride at 120° for ten minutes and then poured into water, *p*-chlorophenol and isobutyric acid were formed. A two-hour period of heating at 140° provided the maximum yield (51%) of the hydroxy ketone which then could be methylated with dimethyl sulfate (70%).

The main side reaction in a Friedel–Crafts reaction with phenol ethers is cleavage of the ether linkage by aluminum chloride. When aluminum chloride was added to a mixture of *p*-bromoanisole and isobutyryl chloride in carbon disulfide, the main product was the demethylated ketone even when the addition was carried out at 5°. The yield of ketonic product was markedly increased and demethylation almost completely eliminated by a modified procedure in which the aluminum chloride was dissolved in nitrobenzene and *p*-bromoanisole was added slowly as the *last* component to the reaction mixture.

Experimental

2-Methoxy-5-chloroisobutyrophenone (I).—*p*-Chlorophenyl isobutyrate[4] (40 g.) prepared in 81% yield from isobutyryl chloride and *p*-chlorophenol, was heated at 140° for two hours with aluminum chloride (30 g.) and nitrobenzene (58 g.). Processing of the reaction mixture produced 22 g. (51%) of material which boiled at 140–

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[1] School of Chemistry, Rutgers University, New Brunswick, New Jersey.

[2] Blatt, in Adams, "Organic Reactions," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 342.

[3] Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936), describe a typical Friedel-Crafts reaction using phenol ethers.

[4] In a single experiment carried out at 110° von Auwers, Baum and Lorenz, *J. prakt. Chem.*, **115** [2], 81 (1927), recovered half of their starting material but did not report the yield of product actually obtained.