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 ($\pm 0.05°$) 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 $\times 10^3$	Reaction ,%	$k \times$ 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 $\ln k = \ln PZ - E/RT$.

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

(1) School of Chemistry, Rutgers University, New Brunswick, New Jersey.

(2) Blatt, in Adams. "Organic Reactions." Vol. I. 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.

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–

142° (18 mm.).[5] The phenolic ketone (84 g.) obtained from several runs was methylated by refluxing for four hours with dimethyl sulfate (44 g.) and 10% sodium hydroxide solution (280 ml.). After processing and fractionation there was obtained 62 g. (70%) of the desired product which boiled at 150–152° (9 mm.).

Anal. Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.16; H, 6.16. Found: C, 62.05; H, 6.26.

The 2,4-dinitrophenylhydrazone melted at 148–149°.

Anal. Calcd. for $C_{17}H_{17}O_5N_4Cl$: C, 51.98; H, 4.36. Found: C, 52.01; H, 4.63.

2-Methoxy-5-bromoisobutyrophenone (II).—Aluminum chloride (60 g.) was dissolved in nitrobenzene (250 ml.) and cooled to −4°. Isobutyryl chloride (48 g.) was added rapidly; then *p*-bromoanisole (84 g.) was dropped in during two hours keeping the temperature at 0°. The mixture was allowed to stir for four hours while the temperature was gradually raised to 15°. Processing produced 74 g. (64%) of the ketone which boiled at 158–163° (10 mm.).

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.10. Found: C, 50.93; H, 5.31.

The 2,4-dinitrophenylhydrazone melted at 154–155°.

Anal. Calcd. for $C_{17}H_{17}O_5N_4Br$: C, 46.70; H, 3.92. Found: C, 46.39; H, 4.21.

When aluminum chloride (100 g.) was added to a mixture of *p*-bromoanisole (106 g.) and isobutyryl chloride (62 g.) in carbon disulfide (1200 ml.) at 5° and the mixture allowed to stand at room temperature for two days, there was obtained after processing 48 g. (35%) of demethylated ketone, b. p. 144–155° (12 mm.). This material was dissolved in sodium hydroxide solution and methylated as for the previous ketone to give II, 44 g. (85%).

(5) von Auwers, Baum and Lorenz, ref. 4, report the boiling point as 130° at 20 mm.

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The Action of 2,4-Dinitrophenylhydrazine on 6-Halogeno-Δ^4-cholestenones

BY D. H. R. BARTON[1] AND E. MILLER

Recently it was reported[2,3] that the action of 2,4-dinitrophenylhydrazine on the 6α- and 6β-chloro- and bromo- Δ^4-cholesten-3-ones in cold methanolic solution afforded an orange compound to which the molecular formula $C_{33}H_{48}N_4O_5$ was assigned. Further examination of this substance has shown that it contains no hydroxyl group (failure to acetylate; no band in infrared), but does contain a C=N grouping and a N–H grouping (infrared maxima at 6.16 and 3.03 μ, respectively, in chloroform solution) and a methoxyl group (Zeisel determination). Having regard to these facts and to the data previously recorded[2,3] we should like to propose the formula 6(α?)-methoxy-Δ^4-cholesten-3-one 2,4-dinitrophenylhydrazone for the orange compound and revise its molecular formula to $C_{34}H_{50}N_4O_5$.

It seems to us that the formulation of this substance is explained somewhat better by the sug-

(1) Harvard University Visiting Lecturer, 1949–1950.
(2) Barton and Miller, THIS JOURNAL, **72**, 370 (1950).
(3) Barton and Miller, *ibid.*, **72**, 1066 (1950).

gestions of Mattox and Kendall[4,5] with regard to the mechanism of the 2,4-dinitrophenylhydrazine reaction with halogeno ketones, at least in ethanol solution, rather than by the alternative proposals of Djerassi,[6] which may apply only for reactions carried out in acetic acid.

Our previous observation[2] that the orange compound was obtained using ethanol and dioxane as solvents must be ascribed to the conditions of working up the reaction product. In each case the orange compound was filtered, washed with the same solvent as had been used for its preparation, and dried. The dry solid was dissolved in a small volume of chloroform and precipitated with methanol. This procedure was repeated once or twice more. The compound thus obtained was dried, dissolved in benzene and chromatographed. It was finally recrystallized very slowly from chloroform–methanol. Presumably etherification or trans-etherification occurred during one of the stages of this involved procedure.[7]

Experimental

For the orange compound prepared as described previously[2]: *Anal.* Calcd. for $C_{34}H_{50}N_4O_5$: C, 68.64; H, 8.48; N, 9.42; Cl, 0.00; OMe, 5.22. Found: C, 68.3[2]; H, 8.3[2]; N, 9.9[2]; Cl, 0.0[2]; OMe, 5.10, 5.17.

(4) Mattox and Kendall, *ibid.*, **72**, 2290 (1950).
(5) We are indebted to Dr. Mattox for kindly sending us a copy of this paper prior to its publication.
(6) Djerassi, THIS JOURNAL, **71**, 1003 (1949).
(7) It is noteworthy that the absorption maximum in the u. v. of the 6-methoxy dinitrophenylhydrazone is somewhat displaced with respect to that for Δ^4-cholestenone dinitrophenylhydrazone.

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The Mannich Reaction with *o*-Phenylphenol

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During the preparation of various Mannich phenols for antimalarial study,[2] three substances were isolated as their hydrochlorides from the reaction between equivalent amounts of 2-phenylphenol, paraformaldehyde and diethylamine. Two of these products are the isomeric α-diethylamino-6-phenylcresols (I and II); the third, α^2,α^4-bis-(diethylamino)-6-phenyl-2,4-xylenol (III), is the exclusive product when an excess of paraformaldehyde and diethylamine is used.[2]

One of the isomeric bases responds to Millon's test for an unsubstituted position ortho to a phenolic hydroxyl group and is therefore assigned the structure II. The other isomer is insoluble in dilute sodium hydroxide and should therefore have the structure I.[2,3] The structure of I was

(1) Department of Pharmaceutical Chemistry, University of Kansas School of Pharmacy, Lawrence, Kansas.
(2) Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).
(3) Decombé, *Compt. rend.*, **196**, 866 (1933).