***d*-5-Ethyl-5-*sec*.-octylbarbituric Acid.**—The procedure was identical with that described above. However, the yield was only 26.5% of the theoretical amount. The product melted at 107°; $[\alpha]^{25}_{\mathrm{D}} = +7°$ (2 g. in 15 cc. of alcohol).

Anal. Subs. 0.2000: 14.8 cc. of 0.1000 *N* HCl. Calcd. for $C_{14}H_{24}O_3N_2$: N, 10.47. Found: 10.36.

***l*-5-Ethyl-5-*sec*.-octylbarbituric Acid.**—This was prepared in exactly the same manner and the yield was identical with that of the dextro compound, $[\alpha]^{25}_{\mathrm{D}} = -7.02°$ (2 g. in 15 cc. of alcohol). In other respects it was identical with the dextro isomer.

Summary

1. The *d*-, *l*- and *dl*-isomers of 5-ethyl-5-*sec*.-octylbarbituric acid have been prepared.
2. Pharmacological tests show that there is almost no difference in physiological action between the *d*- and *l*-isomers.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

CATALYSIS WITH COPPER IN THE ULLMANN REACTION

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Professor Fritz Ullmann[1] discovered that the addition of copper catalyzed the reaction of aryl halides with aryl amines or N-acyl aryl amines to form N-aryl aryl amines and of salts of phenols with aryl halides to form di-aryl ethers. A high boiling solvent (nitrobenzene or phenol) was used and potassium carbonate added to neutralize the halogen acid formed.

In most of the later work a special copper was used as a catalyst. This "Naturkupfer C," is a finely divided product obtained by grinding metallic copper under oil between mill stones. However, in some cases other forms of copper and even copper compounds gave equally good results. There has been little information available to indicate whether the reaction involved a case of heterogeneous or homogeneous catalysis, as to what was the real catalyst and why there was such a variation in the results obtained in using different reactants and different samples of copper or copper compounds.

A rather intensive study has been made of the reaction of phenyl bromide

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[1] (a) Ullmann, *Ber.*, **36**, 2382 (1903); (b) Ullmann and Sponagel, *Ber.*, **38**, 2211 (1905); (c) Irma Goldberg, *Ber.*, **39**, 1691 (1906); (d) *Ber.*, **40**, 4541 (1907); (e) Ullmann, *Ann.*, **355**, 312 (1907); (f) British patents: 2949 (1912), *C. A.*, **7**, 2477 (1913); 16,272 (1910), *C. A.*, **5**, 3121 (1911); 16,440 (1910), *C. A.*, **5**, 3165 (1911); (g) French patent: 418,210 (1910), *C. A.*, **6**, (1912); (h) German patents: 173,523 (1905), *C. A.*, **1**, 513 (1907); 185,663 (1906), *C. A.*, **2**, 351 (1908); 187,870 (1906), *C. A.*, **2**, 602 (1908); 224,982 (1909), *C. A.*, **5**, 213 (1911); 238,106 (1910), *C. A.*, **6**, 1680 (1912); 248,999 (1910), *C. A.*, **6**, 2851 (1912).

with N-acetyl-*p*-toluidine in order to obtain more precise information with regard to the course and mechanism of the reaction which bears Ullmann's name. The yield of N-phenyl-*p*-toluidine resulting from the reaction of phenyl bromide and N-acetyl-*p*-toluidine in nitrobenzene varied from 8 to 43% depending upon whether various forms of metallic copper or copper salts were used. The experimental procedure is given below and a summary of the results under numbers 1–14 inclusive of the table.

TABLE I

THE PREPARATION OF *N*-PHENYL-*p*-TOLUIDINE

Expt.	Catalyst[a]	Solvent	Time, hours	Temp., °C.	Yield, %	Checks	Procedure
1	A	$C_6H_5NO_2$	4	200	38 ± 5	3	1
2	B	$C_6H_5NO_2$	4	200	23 ± 1	2	1
3	C	$C_6H_5NO_2$	4	200	36 ± 2	3	1
4	D	$C_6H_5NO_2$	4	200	25 ± 2	3	1
5	F	$C_6H_5NO_2$	4	200	9 ± 1	3	1
6	H	$C_6H_5NO_2$	4	200	25 ± 5	3	1
7	I	$C_6H_5NO_2$	4	200	23 ± 2	3	1
8	J	$C_6H_5NO_2$	4	200	30 ± 1	3	1
9	K	$C_6H_5NO_2$	4	200	34 ± 3	3	1
10	L	$C_6H_5NO_2$	4	200	22 ± 1	2	1
11	M	$C_6H_5NO_2$	4	200	15 ± 2	3	1
12	N	$C_6H_5NO_2$	4	200	15	1	1
13	O	$C_6H_5NO_2$	4	200	11	1	1
14	P	$C_6H_5NO_2$	4	200	30	1	1
15	A	$C_{10}H_{12}$	4	200	21	1	1
16	A	$C_{10}H_{12}$	8	200	30	1	1
17	A	$C_{10}H_{12}$	24	200	42	1	1
18	A	$C_{10}H_{12}$	48	200	50	1	1
19	A	$C_{10}H_{12}$	148	200	Tar	1	1
20	A	$C_6H_5NO_2$	4	190	21	1	1
21	A	$(C_6H_5)_2O$	4	190	11	1	1
22	A	$(C_6H_5)_2O$	4	200	24	1	1
23	A	$C_{10}H_{12}$	4	190	9	1	1
24	A	$(C_6H_5)_2O$	4	210	39	1	1
25	A	$C_{10}H_{12}$	4	200	5	1	2
26	A	None	15	B. p.	84	1	3
27	A	None	25	B. p.	90	1	3
28	J	None	15	B. p.	87	1	3
29	E	None	15	B. p.	90	1	3
30	A	$C_{10}H_{12}$	4	200	0	2	4
31	A	$C_{10}H_{12}$	4	200	0	2	5
32	A	$C_6H_5NO_2$	4	200	0	2	4
33	A	$C_6H_5NO_2$	4	200	0	2	5
34	A	None	4	B. p.	0	2	6
35	A	None	4	B. p.	0	2	7
36	A	None	4	B. p.	35 ± 10	4	8
37	A	None	4	B. p.	35 ± 10	4	9 (air)
38	A	None	4	B. p.	13 ± 3	3	9 (CO_2)

TABLE I (*Concluded*)

Expt.	Catalyst[a]	Solvent	Time, hours	Temp., °C.	Yield, %	Checks	Procedure
39	E	None	4	B. p.	0	4	9 (CO_2)
40	A′	None	4	B. p.	0	2	9 (CO_2)
41	E	None	4	B. p.	20±3	4	9 (air)
42	A′	None	4	B. p.	20±3	4	9 (air)

[a] CATALYSTS.—(A) "Naturkupfer C." (A′) The "Naturkupfer C" was washed with ether to remove grease, reduced at a dull red heat in a stream of hydrogen and sealed off in the tube in which it was reduced. (B) Metallic copper from the reduction of cupric oxide. (C) Metallic copper from the reduction of cuprous oxide. (D) Metallic copper produced by the action of zinc dust on a concentrated solution of copper sulfate. The copper was washed with dilute hydrochloric acid to remove the zinc and with water until free of acid. It was preserved under water and before use was dried with alcohol and ether. (E) A piece of sheet copper 5 × 5 cm. was washed with ether to remove grease, then with hydrochloric acid to remove the oxide. The acid was washed out with water and the copper dried with alcohol and ether. (F) Commercial cupric chloride crystals were heated to 120° to drive out the water. (G) Commercial cuprous chloride. (H) Commercial cupric bromide. (I) Cuprous bromide, prepared from copper sulfate, potassium bromide and copper wire. (J) Commercial cuprous iodide. (K) Cuprous iodide plus iodine crystals. (L) Cupric oxide was prepared by heating crystalline copper nitrate in a large test-tube until no more brown fumes were evolved. (M) Cuprous oxide was prepared by the reduction of Fehling's solution with dextrose. (N) Commercial cupric acetate. (O) Commercial copper tartrate. (P) Anhydrous copper sulfate.

Procedure 1.—Eight g. (0.05 mole) of acetyl-*p*-toluidine, 8 g. (0.05 mole) of bromobenzene, 5 g. of potassium carbonate, 40 cc. of solvent and the catalytic agent were placed in a 125cc. flask (with a long neck to act as a reflux condenser) and stirred while being heated in the thermostat. After the reaction time had elapsed, the flask was removed from the bath and allowed to cool to room temperature. Almost all of the unreacted acetyl-*p*-toluidine crystallized out. (In order to determine the amount of unreacted material, this was recrystallized from hot water, dried and weighed.) After filtration the solvent was removed by steam distillation. The residue in the flask was shaken with 50 cc. of ether to dissolve the acetylphenyl-*p*-toluidine, the ether layer filtered and the ether removed by distillation. The free amine was obtained by refluxing with 40 cc. of 95% ethyl alcohol and 5 g. of potassium hydroxide for one hour. The hot alcoholic solution was poured into 300 cc. of water and allowed to coagulate sufficiently to make filtration easy. It was dried and weighed.

The reaction is very sensitive to the presence of traces of water and all reagents must be quite dry if a good yield is to be obtained. The yield also depends upon whether nitrobenzene, tetrahydronaphthalene or diphenyl ether is used as a reaction medium (Expts. 1, 15, 22); upon the duration of the heating (Expts. 15, 16, 17, 18, 19); upon the reaction temperature (Expts. 1 and 20, 15 and 23, 21, 22 and 24); and upon the amount of solvent (Expts. 15 and 25). **Procedure 2** was the same as 1 except that 80 cc. instead of 40 cc. of solvent was used.

The failure to obtain higher yields was not due to side reactions which consumed one or the other of the reactants because quantities of both phenyl bromide and acetyl-*p*-toluidine were present in the reaction mixture after the synthetic reaction stopped. The low yields could not be explained on the basis of a reversible reaction because the N-acetylphenyl-*p*-toluidine could not be converted into phenyl bromide and acetyl-*p*-toluidine under the experimental conditions during the synthesis. The use of more copper at the beginning of the synthesis or the addition of a second portion of copper after the first portion ceased to function did not result in increased yields of product. The only conclusion that can be reached from these facts is that the synthetic reaction ceased because the conditions in the reaction mixture became such that a dispersion of catalyst could no longer be maintained. That is to say, the formation of by-products resulted in such a solution that the catalyst was precipitated and further dispersion of copper prevented. The variation of the yields of secondary amine with variations in kind and amount of solvent, source of catalyst and concentration of water are in agreement with this conclusion, for the time required for the solution to become "poisoned" would depend upon the solvent and its impurities, such as water, and upon the impurities and catalysts for side reactions introduced along with the copper from various sources.

The picture of the reaction would then include the fact that almost any copper or copper compound may be used as a source of catalyst but that the true catalyst becomes dissolved or dispersed in the reaction mixture and catalyzes the reaction until it is thrown out of solution due to the development of a sufficient concentration of impurities.

To test out these ideas the reaction was then run without a solvent even though all previous workers had recommended the use of one. The yields so obtained were more than double the best yields obtained with the best solvent (Runs 26–29 inclusive).

Procedure 3.—Four g. of acetyl-*p*-toluidine, 4 g. of bromobenzene, 2.5 g. of potassium carbonate and the catalyst were placed in a 50cc. Erlenmeyer flask fitted with a 30cm. reflux air condenser, and boiled vigorously on an electric hot-plate. After the reaction time had elapsed, 5 cc. of water was added and steam bubbled through to remove the excess bromobenzene. After cooling, the product was extracted with 30 cc. of ether, filtered, the ether evaporated off and the *N*-acetylphenyl-*p*-toluidine hydrolyzed as in Procedure 1.

The question then arises as to whether the catalyst is a dispersed solid or is in true solution and, if the latter, which one or combination of reactants is responsible for carrying the copper or copper compound into a soluble form. The following experiments were carried out.

Procedure 4.—Eight g. of acetyl-*p*-toluidine, 5 g. of potassium carbonate, 40 cc. of solvent and the catalyst were stirred while being heated for two hours in the thermostat. The hot mixture was filtered to remove the copper, and to the liquid were added 8 g. of bromobenzene and 5 g. of potassium carbonate (thereafter Procedure 1).

Procedure 5.—The catalyst, 40 cc. of solvent, 8 g. of bromobenzene and 5 g. of potassium carbonate were stirred while being heated in the thermostat for two hours. The hot solution was filtered to remove the copper and to it were added 8 g. of acetyl-*p*-toluidine and 5 g. of potassium carbonate (Procedure 1 thereafter).

Procedure 6.—The catalyst, 8 g. of acetyl-*p*-toluidine and 5 g. of potassium carbonate were heated together at about 200° for two hours in a 50cc. Erlenmeyer flask. The product was dissolved in dry benzene, the copper filtered off and the benzene evaporated. Five g. of potassium carbonate and 8 g. of bromobenzene were added (thereafter Procedure 3).

Procedure 7.—The catalyst was refluxed with 8 g. of bromobenzene and 5 g. of potassium carbonate for two hours. The mass was dissolved in a little benzene and filtered to remove the copper. After distilling off the benzene, 8 g. of acetyl-*p*-toluidine and 5 g. of potassium carbonate were added (thereafter Procedure 3).

Procedure 8 was the same as 6 except that the material after heating was dissolved in boiling absolute alcohol instead of benzene. The extract was red in color. When 95% alcohol was used for the extraction, the dried, extracted material gave lower yields of *N*-phenyl-*p*-toluidine than that extracted with absolute alcohol. This indicates that the deleterious effect of water upon the Ullmann reaction is due to its partially destroying the intermediate copper compound.

The results of these experiments (see Table I) showed very conclusively that none of the reactants had any effect upon copper in converting it into a catalyst except the acetylated amine. This reacted with either Naturkupfer C or sheet copper to form an alcohol soluble compound. This alcohol soluble compound was active in promoting the reaction of bromobenzene and N-acetyl-*p*-toluidine. If air was excluded during the fusion of the acetylated amine over sheet copper the alcoholic extract contained no catalyst. However, the exclusion of air from the fusion of N-acetyl-*p*-toluidine with Naturkupfer C (Run 38) did not entirely prevent the formation of an alcohol soluble catalyst. However, Naturkupfer C failed to yield a catalyst if before fusion with the acetylated amine it was washed with ether to remove grease and heated in a stream of hydrogen to remove adsorbed oxygen (Expt. 40). Both sheet copper and the washed and deoxygenated Naturkupfer C yielded a catalyst if air was used as in Procedure 9 (Expts. 41, 42).

Procedure 9.—The catalyst was fused with 8 g. of acetyl-*p*-toluidine in a 50cc. Erlenmeyer flask at about 200° for two hours. It was dissolved in boiling absolute alcohol and filtered. The alcohol was boiled away and 8 g. of bromobenzene and 5 g. of potassium carbonate were added (thereafter Procedure 3). In order to carry out this reaction in an atmosphere of carbon dioxide, the gas was passed through the flask containing the catalyst and acetyl-*p*-toluidine in order to drive out the air. The pressure was lowered to 30 mm. and the flask was heated at 200° for two hours. Air was allowed to enter, alcohol added, and the process carried out as above. If the mixture was heated so high that the acetyl-toluidine began to distil, only tarry matter was formed. If the temperature was much below 200°, a long time was required for the reaction.

It is clear, then, that the catalyst for the Ullmann reaction is formed by the reaction of copper with the acetylated amine in the presence of air, and that it is, in the case investigated, an alcohol soluble compound which is either red in color or associated with such a compound. The fact that copper reacts with oxygen and ammonia to form $Cu(NH_3)_4(OH)_2$[2] perhaps gives a hint as to the constitution of the catalytically active copper derivatives of the acetylated amine.

In order to obtain the maximum yield of N-phenyl-*p*-toluidine, at least 0.1 g. of copper must be used for 0.05 mole of reactants. In order to be sure of having enough, 0.3 g. was used in most of the preparations. The alcohol extract containing the true catalyst used in Expts. 36 and 37 contained the equivalent of approximately 2 milligrams of copper. It may be noted that the yields were considerably lower in these cases than in those where metallic copper was present during the reaction of the N-acetyl amine and the phenyl bromide. This is probably due to the fact that the true catalyst is gradually destroyed during the course of the reaction and if no metallic copper is present there is no replenishment of the supply of true catalyst by solution of metallic copper. The use of only a portion of the alcoholic extract of Procedure 8 resulted in lower yields than were obtained by the use of the whole extract.

Magnesium oxide, calcium carbonate, *p*-toluidine and quinoline were substituted for the potassium carbonate in the procedure for the preparation of N-phenyl-N-acetyl-*p*-toluidine but no reaction ensued. All attempts to use powdered metallic silver, silver iodide or silver oxide in place of copper gave negative results as reported by Ullmann. Naturkupfer C apparently does not promote the reaction of butyl or phenyl bromide with phthalimide. However, a small amount of diphenylamine was formed by the reaction of acetamide with phenyl bromide. N-phenyl-*o*-toluidine (b. p., 304–305°, corr.) was prepared in 70% yield by the reaction of 0.2 mole of N-acetyl-*o*-toluidine with 0.2 mole of phenyl bromide *without* a solvent in the presence of Naturkupfer C. The N-acetyl-N-phenyl-*o*-toluidine obtained as an intermediate apparently had not previously been prepared. It has a melting point of 77.5°, the crystals

Table II

The Preparation of Diphenyl Ether

Expt. no.	Catalyst	Solvent	Time, hours	Temp., °C.	Yield, %	Checks	Procedure
43	A	C_6H_5OH	2	210	70	2	10
44	A	C_6H_5OH	3	210	60	2	11
45	None	C_6H_5OH	3	210	0	1	11
46	A	None	3	210	0	2	11
47	E	C_6H_5OH	4	210	50	1	11
48	E	C_6H_5OH	5	210	30	2	12 (air)
49	E	C_6H_5OH	5	210	0	2	12 (CO_2)

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[2] Yamasaki, *Science Repts. Tokoku Univ.*, 9, 169 (1920); Dawson, *Z. physik. Chem.*, 69, 110 (1909).

being triclinic. Templeton[3] was unable to prepare N-phenyl-*o*-toluidine using nitrobenzene as a solvent. His negative results have been checked.

A summary of the results obtained in using copper as a catalyst for the reaction of potassium phenoxide and phenyl bromide is shown in Table II, the experimental procedures being given below.

Procedure 10.—Four g. of metallic potassium was dissolved in 17 g. of melted phenol, keeping the mass hot enough so that it remained liquid. Some charring took place. To this were added 15.8 g. of bromobenzene and the catalyst and the mixture was heated under a reflux condenser in an oil-bath. After cooling, 120 cc. of water and some potassium hydroxide were added to dissolve the phenol and phenoxide. The diphenyl ether was separated, dried with anhydrous sodium sulfate and distilled. Depending on the yield of diphenyl ether obtained, the layer containing it might be on top or below.[4]

Procedure 11.—Thirteen g. of potassium phenoxide, 15.8 g. of bromobenzene, 10 g. of phenol and the catalyst were heated together under a reflux air condenser in an oil-bath. The products were separated according to Procedure 10.

Procedure 12.—The catalyst and 10 g. of phenol were heated together at 150–160° for two hours while air was slowly passed through the mixture. The phenol was poured away from the catalyst, and to it were added 15.8 g. of bromobenzene and 13 g. of potassium phenoxide. Thereafter the procedure was the same as in number 10, carbon dioxide being used as in Procedure 9.

These experiments show that air is necessary for the formation of an active catalyst from copper and phenol as it is in the case of N-acetyl-*p*-toluidine. Contrary to the experience of Ullmann, there was found to be no great difference in the yield of diphenyl ether irrespective of whether the phenoxide was made by the reaction of potassium hydroxide or phenol or by the reaction of potassium and phenol as recommended by Ullmann. It is, however, necessary that excess phenol be used as a solvent for the reaction and that water be excluded from the reaction mixture. The true catalyst appears to be a combination of phenol and copper which is sensitive to the presence of water.

Preparation and Purity of Reagents

Acetyl-*p*-toluidine and Acetyl-*o*-toluidine were prepared by the action of acetic anhydride on the corresponding toluidines. The products after recrystallization had melting points of 150.5° (corr.) and 110° (corr.), respectively.

The **bromobenzene** was dried over calcium chloride; b. p., 154–155.5° (corr.).

The **potassium carbonate** was dried at 200° for ten hours.

The **solvents** were dried with calcium chloride and distilled: nitrobenzene, b. p., 209.5–211° (corr.); diphenyl ether, b. p., 258–261° (corr.); tetrahydronaphthalene, b. p., 205–208° (corr.).

The **potassium phenoxide** was prepared by dissolving potassium hydroxide in fused phenol. The water and excess phenol were removed by distillation under a pressure of 30 mm. at 210° for three hours.

The other reagents used were the usual commercial products.

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[3] Templeton, Ph. D. *Dissertation*, Wisconsin, **1924**.

[4] Ullmann and Sponagel, *Ann.*, **350**, 83 (1906).

Summary

It has been found that the addition of almost any sample of metallic copper or copper compound will catalyze the reaction of phenyl bromide and N-acetyl-*p*-toluidine. The yield of product varies and is a function of the particular sample of copper or copper compound used. It also varies with the kind and amount of solvent as well as with the dryness of the reagents.

The use of a solvent as by former workers is quite disadvantageous, the yields without a solvent being more than twice as great as under the optimum conditions with a solvent. N-phenyl-*o*-toluidine could not be obtained using nitrobenzene as a solvent but was easily obtained in 70% yield without a solvent.

The low yields in a solvent are not due to a reversal of the reaction or to side reactions but are apparently due to the fact that conditions in the reaction mixture become such that it is no longer possible for a concentration of the true catalyst to be maintained. Direct evidence on this point has been obtained with respect to the injurious action of water.

It has been shown that copper reacts with N-acetyl-*p*-toluidine only in the presence of air to form an alcohol soluble compound which is apparently the true catalyst for the Ullmann reaction. An amount of this compound containing two milligrams of copper will catalyze the reaction of 0.05 mole of each of the reactants to a 35% yield.

"Naturkupfer C" gave no better yields than cuprous iodide or sheet copper for the reaction where no solvent was used. It was no better than copper reduced from the oxide or cuprous iodide when nitrobenzene was used as a solvent.

Phenol, copper and air form an active catalyst for the reaction of potassium phenoxide and phenyl bromide. The presence of phenol as a solvent is apparently necessary for this preparation.

It has not been found possible to substitute carbonates or bases for sodium or potassium carbonate or to use silver as a catalyst or to catalyze the reaction of phthalimide with phenyl or butyl bromide.

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