drochloride, 10.0 ml. of propionic anhydride and 2.0 ml. of triethylamine was heated at 85–90° for 16 hours. The reaction solution was concentrated *in vacuo* and the residue was dissolved in 50 ml. of water. After washing with ether, the aqueous solution was made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether, washed with three 25-ml. portions of cold water, and then dried over anhydrous magnesium sulfate. The ether was distilled and the α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane recrystallized two times from petroleum ether; m.p. 75–76°, weight 3.6 g., $[\alpha]^{25}D$ +67.3° (*c* 0.6 in chloroform).

Anal. Calcd. for $C_{22}H_{29}NO$: C, 77.83; H, 8.62. Found: C, 77.71; H, 8.61.

The hydrochloride salt was prepared in ether using anhydrous hydrogen chloride. The α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride after three recrystallizations from methanol–ethyl acetate melted at 163–164°, $[\alpha]^{25}D$ +59.8° (c 0.6 in water).

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot HCl$: C, 70.28; H, 8.04. Found: C, 70.47; H, 8.07.

α-*l*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane Hydrochloride.—A solution of 3.0 g. (0.0094 mole) of α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, 4.0 ml. of pyridine and 8.0 ml. of propionic anhydride was refluxed for five hours. The excess propionic anhydride, propionic acid and pyridine were removed *in vacuo* and the residue dissolved in water. After washing once with ether, the aqueous solution was made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether and dried over anhydrous magnesium sulfate. The ether was distilled and the α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane recrystallized two times from petroleum ether; m.p. 75–76°, weight 1.9 g., $[\alpha]^{25}D$ −68.2° (*c* 0.6 in chloroform).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.83; H, 8.62. Found: C, 77.65; H, 8.62.

The hydrochloride salt was prepared in ether solution using anhydrous hydrogen chloride. The α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride after three recrystallizations from methanol–ethyl acetate melted at 163–164°, $[\alpha]^{25}D$ −60.1° (*c* 0.7 in water).

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot HCl$: C, 70.28; H, 8.04. Found: C, 70.28; H, 8.07.

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Arylation of Unsaturated Systems by Free Radicals. IV.[1] Effects of Catalyst, *p*H and Solvent upon the Meerwein Reaction

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The Meerwein reaction involves arylation of a conjugated unsaturated system by a diazonium salt in a buffered aqueous acetone solution at *p*H 3 in the presence of cupric chloride.[3] The effect of the structure of the diazonium salt has been investigated by several workers[3] and the effect of the nature of the unsaturated constituent is now under investigation. However, no systematic study of the numerous other variables has been recorded.

In this work we report the effects of varying the metal catalyst, the solvent, the *p*H and the buffer ingredients. The reaction of *p*-nitrobenzenediazonium chloride and coumarin was selected for study since good yields can be obtained using the "standard" conditions outlined by Meerwein,[4] and the product is easily isolated. A standardized procedure was adopted and the variables were changed one at a time. The results are presented in Tables I–IV.

Cupric chloride is by far the most effective catalyst. Slight catalytic activity was noted with zinc, cadmium and mercuric salts, as well as with copper powder, when compared to the results in blank runs with no added catalysts. The remarkable activity of cupric salts appears to be derived from the "irregularity" in the electronic configuration of copper. It should be noted that small yields are obtained even in the absence of catalyst. This may be a measure of the simple radical process suggested by Koelsch[5] and Müller.[6]

Acetone was the best solvent, followed by acetonitrile. Unsaturation in the solvent exerts a beneficial effect upon the Meerwein reaction, indicating that the solvent is involved in some fundamental way in the intermediate complex.[1,3]

Table III emphasizes the *p*H dependence; the best results in an acetate buffer were obtained at *p*H 2–4. At low *p*H, competition with the Sandmeyer reaction becomes important, while at *p*H 5 the resinous character of the crude product points out the other modes of decomposition available to the diazonium salt.

It was surprising to note the dependence on buffer composition at constant *p*H 3. Acetate is the best; Meerwein's report[4] indicates that chloroacetate is similar in behavior. Perhaps the succinate results derive from an entropy difference in forming the intermediate complex with the large acid; alternatively, since acetic acid is weaker than succinic, the difference may reflect merely the fraction dissociated. Addition of cupric complexing agents, as expected, reduces the catalyst efficiency markedly, the effect being least with citrate and greatest with ethylenediaminetetraacetic acid (Versene).

Experimental

Catalyst Experiments.—*p*-Nitroaniline (0.03 mole) was diazotized with 25 ml. of 1:1 hydrochloric acid, 15 g. of ice and 7.0 ml. of 30% sodium nitrite solution. Sodium acetate was added to give *p*H 4 (*p*H paper), followed by 75–90 ml. of acetone and 0.03 mole of coumarin. Finally 0.0045 mole of the catalyst was added to the solution maintained at 0–5°. After stirring until nitrogen evolution was complete, the mixture was steam distilled. The water-insoluble residue in the flask was collected by filtration, washed with water and acetone (3-*p*-nitrophenylcoumarin is almost insoluble in acetone), and recrystallized from anisole (10–12 ml. per gram). The crude melting points are given in Table I as an indication of purity; once-recrystallized material generally melted at 262–264°.

When the reaction mixture was worked up by evaporating the acetone without heating, the yields were lower. Perhaps an intermediate chloro compound is formed to some extent, and it is lost during the acetone washing, whereas steam distillation converts it to 3-*p*-nitrophenylcoumarin.

Solvent Dependence.—*p*-Nitroaniline (0.03 mole) was diazotized as before. The *p*H was adjusted to 3.5 (short-range *p*H paper) with sodium acetate, and 0.0045 mole of $CuCl_2$ was added. This solution was then added to 0.03 mole of coumarin in 90 ml. of the solvent at 0–5°. After

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[1] Paper III, O. Vogl and C. S. Rondestvedt, Jr., THIS JOURNAL, **77**, 3067 (1955).

[2] On leave from University of Vienna, Austria.

[3] For a literature survey, see C. S. Rondestvedt, Jr., and O. Vogl, *ibid.*, **77**, 2313 (1955).

[4] H. Meerwein, E. Buchner and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

[5] C. F. Koelsch and V. Boekelheide, THIS JOURNAL, **66**, 412 (1944).

[6] E. Müller, *Angew. Chem.*, **61**, 179 (1949).

TABLE I

EFFECT OF METAL SALTS UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Salt	Crude yield, %	M.p., °C.	Recrystn. yield, %
$CuCl_2$	44	257–259	37
$FeSO_4$	15	260–262	7
$MnCl_2$	11	256–259	11
$ZnCl_2$	21	254–258	18
$NiCl_2$	11	250–255	9
$CoCl_2$	11	258–261	10
$HgCl_2$	26, 27	254–258	22
$HgCl_2$[a]	9	262–265	..
H_2PdCl_4	8	259–262	6
MgO	9	254–258	7
$CdCl_2$	19, 21	256–261	16
$CdCl_2$[a]	9	256–258	..
$SnCl_2$	5	260–262	4
$Pb(OAc)_2$	16	255–257	8
$CrO_3 + Na_2SO_3$	6	260–262	5
$AlCl_3$	12	242–250	9
$FeCl_3$	16	259–261	10
$KMnO_4$	8	254–256	7
$Na_2Cr_2O_7$	13	261–263	8
None (blank)	11	255–258	8
Cu powder[a]	16	258–260	..
None (blank)[a]	9	...	..

[a] *p*H adjusted to 3.5 ± 0.05 with a *p*H meter. Worked up by removing volatiles *in vacuo* without heating.

nitrogen evolution was complete, the solvent was removed *in vacuo* without heating, or by steam distillation. The product was washed with water and acetone, then recrystallized from anisole.

TABLE II

EFFECT OF SOLVENTS UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Solvent	Crude yield, %	Crude m.p., °C.	Recrystn. yield, %
Acetone	41[a]	257–260	38
Acetone	44[b]	248–253	..
Acetonitrile	26[a]	259–261	23
Acetonitrile	34[b]	248–253	..
Tetrahydrofuran	5[a]	264–265	5
Tetrahydrofuran	23[b]	256–259	..
Dimethylformamide	19[c]	261–264	17
Dimethylformamide	26[b]	251–255	..
Ethanol	8[a]	257–258	4
Glycol dimethyl ether	23[a]	258–260	21
Glycol dimethyl ether	26[b]	253–257	..

[a] Worked up by evaporating solvent *in vacuo*. [b] Worked up by steam distillation. [c] The insoluble product was collected by filtration; a second crop was obtained by steam distilling the filtrate.

***p*H Experiments.**—*p*-Nitrobenzenediazonium chloride (0.03 mole), prepared as before, was brought to the desired *p*H by addition of sodium acetate solution. Cupric chloride (0.0045 mole) was added and the *p*H was again adjusted (*p*H meter). The solution was added to 0.03 mole of coumarin and 90 ml. of acetone. The product was worked up as before, without heating.

TABLE III

EFFECT OF *p*H UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

*p*H	Crude yield, %	Crude m.p., °C.	Color crude	Recrystn. yield, %
1	22	258–260	Yellow	21
2	30	257–260	Yellow	28
3	35	258–261	Yel.-brown	30
4	30	251–256	Dark brown	27
5	17	250–256	Black	15

Buffer Experiments.—*p*-Nitroaniline (0.03 mole) was diazotized as before. The filtered solution was brought to *p*H 3 ± 0.05 (*p*H meter) by addition of a concentrated solution of the appropriate sodium salt. Cupric chloride (0.0045 mole) was added and the *p*H again was adjusted. The solution then was added to a cold solution of 0.03 mole of coumarin in 90 ml. of acetone. Nitrogen evolution commenced immediately. The solution was stirred while the ice-bath melted and allowed to stand overnight. After removal of the solvent *in vacuo*, the precipitate was washed with water, dried, and stirred with acetone. It was then recrystallized from anisole.

TABLE IV

EFFECT OF BUFFER COMPONENT UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Buffer	Crude yield, %	Crude m.p., °C.	Recrystn. yield, %
Acetate	40–45	257–260	33–40
Succinate	21	258–260	19
Citrate	28	252–256	24
Citrate	26	253–258	23
Versene	7	257–260	6
Tartrate	13	253–258	11
Phosphate	13	251–256	11

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1-Aryloxy-3-[N-heterocyclicamino]-2-propanols[1]

BY C. B. POLLARD AND R. W. INGWALSON

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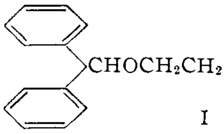
In recent years numerous pharmacological investigations have resulted from the synthesis of alkylamine ethers of phenols and arylalkanols and the synthesis of amino alcohols due to the discovery of the potent antihistaminic action of benzhydryl β-dimethylaminoethyl ether [Benadryl (I)] and many of its derivatives.[2] Because of this physiological activity of basic ethers and basic alcohols,



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[1] This paper is abstracted from a portion of a dissertation submitted by Raymond W. Ingwalson to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1952.

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