TABLE VI

REARRANGEMENTS OF THE ENOL BENZOATES, II AND ITS DERIVATIVES, IN DIOXANE AT 97.10 ± 0.02°

Substituent	Init. concn., moles/l	Wave length, mμ	10^5k_1, sec.$^{-1}$
None	0.0017	470	1.49 ± 0.02
	.0020	470	1.46 ± 0.02
	.0012	470	<2.3[a]
p-Methoxy	.0010	475	1.13 ± 0.004
	.00065	470	1.20 ± .01
p-Nitro	.0010	515	14.5 ± .07
	.0017	515	14.0 ± .04

[a] Reaction in dioxane–water (80:20). The calculated rate constants drifted from 2.23 to 1.73 and since it was suspected that solvent escaped in this experiment the value of 2.3 is taken as an upper limit for the rate constant.

compartment. Routine checks at the beginning and end of several experiments showed that the temperature of the solutions was controlled to better than 0.5°. Other experiments were carried out in a jacketed 5-cm. cell with water from a constant temperature bath circulating through the jacket. 1-Benzeneazo-2-naphthol, m.p. 133.5–134.5° (lit.[39] 134°), was purified by crystallization from ethanol. Its visible spectrum in dioxane showed λ_{max} 472 mμ (ε 14,300) at concentrations of 10^{-5} to 10^{-4} *M*. 1-Benzeneazo-2-naphthylamine, m.p. 100–100.5° (lit.[40] 102–104°), crystallized from acetic acid-water, had λ_{max} 448 mμ (ε 13,600) at the same concentrations as the azonaphthol. Disodium 1-benzeneazo-2-naphthol-3,6-disulfonate, bright red crystals, m.p. 310°, showed λ_{max} (ε 18,500) at the same concentrations. Reactions were followed by measuring absorbances at 472, 450 and 490 mμ for the couplings with the naphthol, naphthylamine and R salt, respectively. Rate constants were obtained from a plot of log $(A_\infty - A_0)/(A_\infty - A)$ against *t*. When the plot showed curvature the initial slope was estimated. Otherwise the slope was obtained by the method of least squares. Sample data are presented in Table VII.

TABLE VII

RATE OF REACTION OF BENZENEAZOTRIBENZOYLMETHANE WITH R SALT IN DIOXANE–WATER (86:14) AT 27.4 ± 0.05°[a]

Time, min.	*A*	10^4k, sec.$^{-1}$	Time, min.	*A*	10^4k, sec.$^{-1}$
0	0.122	17.47	12	0.583	16.23
2	.248	16.42	14	.617	16.32
4	.339	16.38	16	.648	16.25
6	.418	16.37	18	.672	16.38
8	.484	16.67	20	.694	
10	.542	16.42		.787[b]	

[a] Initial concentrations were 1×10^{-5} *M* azotriketone and 1×10^{-4} *M* R salt. [b] Experimental value measured after 10 half-times.

TABLE VIII

COUPLING OF BENZENEAZOTRIBENZOYLMETHANE AND R SALT IN DIOXANE–WATER MIXTURES

Temp., °C.	Water,[a] %	[R salt]/[I]	10^4k, sec.$^{-1}$
27.4[b]	12	10	15.00 ± 0.05
27.4[b]	12	20	14.37 ± .08
27.4[b]	14	10	16.27 ± .05
27.4[b]	14	20	18.07 ± .11
28.0[c]	15	10	16.70 ± .04
27.0[c]	50	100	52.6 ± 1.3

[a] Here *x*% water refers to a solution made by diluting (100 − *x*) ml. with *x* ml. of water to a total volume of 100 ml. [b] ± 0.05°. [c] ±0.5°.

(39) C. Liebermann, *Ber.*, **16**, 2860 (1883).
(40) T. A. Lawson, *ibid.*, **18**, 798 (1885).

[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Metal-ion Sensitive Protecting Groups in Synthesis. The Carbo-(8-quinoloxy) Substituent and its Removal by Accelerated Hydrolysis[1]

BY E. J. COREY AND ROBERT L. DAWSON

RECEIVED AUGUST 2, 1962

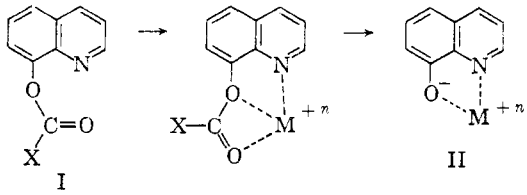
The use of the carbo-(8-quinoloxy) group for the protection of amino nitrogen is described together with details concerning its detachment by means of metal-ion accelerated hydrolysis.

The "blocking" groups which are in common use for the protection of functions such as amino and hydroxyl from electrophilic attack during synthesis are invariably removed by use of an acid, a base or a reducing agent.[2] The objective of the present study was the development of a blocking group which could be dislodged under essentially neutral conditions and without the use of reducing or oxidizing reagents. Obviously, such a protecting group might be uniquely useful in certain highly restrictive synthetic situations. In particular, our scheme entailed as its central feature the employment of a protecting group which is extremely susceptible to metal-ion promoted hydrolysis but relatively resistant to hydrolysis in the absence of metal ion. There exists ample indication that for suitable structures an enormous acceleration of ester or amide hydrolysis by a complexing metal ion is possible. Thus, the hydrolysis of α-amino acid esters (*e.g.*, glycine ethyl ester) proceeds rapidly in aqueous solution in the presence of amino-coordinating transition metal ions (*e.g.*, Cu^{++}) under circumstances which do not lead to appreciable hydrolysis in the absence of the metal cation.[3] In addition, it is known that 0.1 *M* Cu^{++} increases the rate of hydrolysis of glycine amide at *p*H 7.9–9.25 by a factor of at least 100.[4] It appears probable in these cases that coördination occurs between the metal cation and the α-amino group and also the nearby carbonyl group which is positioned to allow weak chelation. This complex should be relatively susceptible to nucleophilic carbonyl addi-

(1) From the Ph.D. dissertation of R. L. D., Harvard University, (1961).
(2) For reviews of such protecting groups as applied to peptide synthesis see (a) W. Grassman and E. Wunch, *Fort. Chem. Org. Nat.*, **13**, 444 (1956), and T. Wieland and B. Heinke, *Angew. Chem.*, **69**, 362 (1957).
(3) H. Kroll, *J. Am. Chem. Soc.*, **74**, 2036 (1952).
(4) L. Meriwether and F. H. Westheimer, *ibid.*, **78**, 5119 (1956).

tion with subsequent cleavage to form a more stable α-amino acid metal chelate.

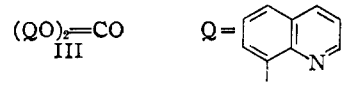
The specific blocking group selected for our initial study was the carbo-(8-quinoloxy) unit (I). It is



I II

apparent that this system is capable of coördination with a metal ion at nitrogen and simultaneously at one or both of the neighboring oxygens and also that a complex of 8-hydroxyquinoline anion (II), known to be very stable for metal ions such as Cu^{++} and Ni^{++},[5] results after hydrolysis of the phenolic ester linkage. From these considerations we were led to suppose that the carbo-(8-quinoloxy) group could be applied to the protection of amino nitrogen, and possibly to peptide synthesis, and that the normally unreactive urethan system (X = NH) could be hydrolyzed under extremely mild conditions.

The synthesis of N-carbo-(8-quinoloxy) derivatives of amines was accomplished by using bis-(8-quinolol) carbonate (III), a stable crystalline substance readily prepared from 8-quinolol and phosgene, as the acylating agent. These acylation reactions were generally conducted in methylene chloride solution at 0° with satisfactory results except in those cases where the amino component was highly insoluble, *e.g.*, free amino acids.



III

The hydrolysis of carbo-(8-quinoloxy) derivatives of amines was indeed found to be greatly accelerated by metal ions and, as expected, Cu^{++} and Ni^{++} were unusually effective. Most of these reactions were carried out at *ca.* 25° in 50% aqueous acetone (or alternatively a 50% aqueous mixture with other water-miscible solvents) and *most appeared to be complete after 15–60 minutes* in the presence of one-half mole of Cu^{++} or Ni^{++} per mole of carbo-(8-quinoloxy) compound. Table I summarizes some of the data on these metal-ion accelerated hydrolyses which, of course, produced the amine salts rather than unstable carbamic acids. The yields which are given are based on isolated amine or

$$QOCONHR + {}^1/_2Cu^{++} + H_2O \longrightarrow (QO)Cu/2 + CO_2 + RNH_3^+$$

amine salt and it is probable that the reaction efficiencies are considerably better.

TABLE I

METAL-ION CATALYZED HYDROLYSIS OF CARBO-(8-QUINOLOXY) DERIVATIVES

Compound	Metal ion	Yield, %
$QOCONHC_6H_5$	Cu^{++}	60
$QOCONHCH_2COOC_2H_5$	Ni^{++}	58
$QOCONHCH_2CONHCH_2C_6H_5$	Cu^{++}	73
$QOCO(NHCH_2CO)_2NHCH_2C_6H_5$	Cu^{++}	69

(5) See, "Stability Constants," Part I, Chem. Soc. London Special Publ. No. 6.

An interesting situation was encountered in the metal-ion accelerated hydrolysis of carbo-(8-quinoloxy)-glycinanilide (IV) in that coördinating metal ion accelerated not only the hydrolysis to glycinanilide (V) but also intramolecular nucleophilic attack to form the hydantoin VI.

$$QOCONHCH_2CONHC_6H_5 \longrightarrow$$

IV

$$H_3N^{\oplus}CH_2CONHC_6H_5 \text{ or } \underset{HN \quad NC_6H_5}{\overset{CH_2—CO}{\diagup \quad \diagdown \quad \diagup}} + H^+$$

V VI

$$+ H_2O + {}^1/_2M^{++} + {}^1/_2(QO)_2M$$

The proportion of anilide V to hydantoin VI was strongly dependent on the nature of the cation *and* anion in the salt used and on certain other reaction conditions, *e.g.*, solvent and *p*H. Thus, with cupric acetate in aqueous acetone as solvent the only isolable product was the hydantoin (92.5% yield), but with cupric tosylate under essentially the same conditions the anilide and hydantoin were obtained in approximately equal amount. The tosylate salts of Ni^{++}, Cu^{++} and UO_2^{++} generally afforded at least as much anilide salt as hydantoin; the tosylate salts of Mg^{++} and Fe^{++}, on the other hand, gave only hydantoin. The formation of 3-phenylhydantoin appeared to occur exclusively in acid- or base-catalyzed hydrolysis in the absence of coördinating metal ion. Because of the obvious complexity of this case and because hydantoin formation did not appear to be important except for the anilide system, the problem of hydantoin *vs.* amine formation from IV was not studied in greater detail and is still unclear. Nonetheless, our results do indicate that even for those carbo-(8-quinoloxy) derivatives such as IV which tend to give cyclic products in the metal-ion promoted cleavage some control can be exercised over the products by selection of experimental conditions.

Application of the carbo-(8-quinoloxy) group to peptide synthesis can in principle be made in a number of ways, one of the simplest of which is the process: amino acid → N-carbo-(8-quinoloxy)-amino acid → carboxyl activated N-carbo-(8-quinoloxy)-amino acid derivative → N-carbo-(8-quinoloxy) peptide → homopeptide. A model demonstration of such a scheme has been carried out as shown for the preparation of phenylalanine cyclohexylamide. Good yields were obtained

$$(QO)_2CO + C_6H_5CH_2\underset{NH_3^+}{\underset{|}{CH}}—COO^- \longrightarrow$$

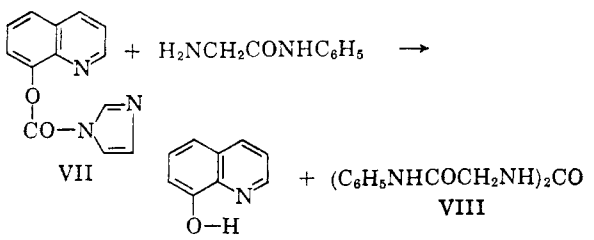
$$QOCONHCHCOOH$$
$$\quad\quad |$$
$$\quad\quad CH_2C_6H_5$$
$$R\text{–}NH_2 \downarrow \text{ Woodward reagent}$$
$$QOCONHCHCONHR$$
$$\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad CH_2C_6H_5$$
$$\quad\quad\quad\quad Cu^{++}$$
$$(QO)_2Cu + CO_2 + H_2NCHCONHR \longleftarrow$$
$$\quad\quad\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad\quad\quad CH_2C_6H_5$$

R = cyclohexyl; Q = 8-quinolyl

without extensive experimentation except for the first step. The introduction of the carbo-(8-quino-

loxy) grouping had to be carried out in aqueous medium for solubility reasons and under these conditions with equimolar amounts of amino acid and bis-(8-quinolyl) carbonate only 33% yield of the carbo-(8-quinoloxy) derivative was realized. It seems likely that appreciable hydrolysis of the carbonate intervenes and that an excess of this reagent would have to be employed for efficient conversion of amino acid.

In connection with the development of alternative methods for the attachment of the carbo-(8-quinoloxy) grouping to an amino function, the imidazole derivative VII was prepared from 8-quinolol and N,N'-carbonyldiimidazole.[6] Interestingly, however, the reaction of VII with glycinanilide gave only the symmetrical urea derivative VIII. It may be that VIII is formed by way of carbo-imidazolylglycinanilide since a control experiment revealed that carbo-(8-quinoloxy)-glycinanilide reacts only slowly with glycinanilide under corresponding conditions. It would appear that after carbonyl addition to VII, a proton be-



comes attached to the 8-quinoloxy group rather than the imidazolyl moiety with the consequence that the former group is eliminated. This observation is especially striking when the great susceptibility of N,N'-carbonyldiimidazole to CO–N fission is considered.

In conclusion a few general remarks on metal-ion sensitive protecting groups and their possible place in synthesis appear to be warranted. It is abundantly clear that groups such as 8-quinoloxy, which are converted to very stable metal chelates after hydrolysis and which have one (or more) coördinating groups before cleavage, can be removed under remarkably mild conditions. However, the development of this technique as a synthetic method requires consideration of a number of factors beside ease of removal. These include efficiency and convenience in the attachment of the blocking group and stability of the group during all the necessary reactions and operations prior to its detachment. It is obvious, for instance, that the carbo-(8-quinoloxy) grouping is too reactive for the protection of hydroxyl functions. Fortunately, there are a great variety of structures which could serve as metal-ion sensitive protectors; *e. g.*, structures based on the 1,10-phenanthroline system, the pyridine system or even thio ethers. Full exploitation of the metal-ion removable group in synthesis requires further study; additional research along these lines is now in progress in our laboratories using the experience from the investigation reported herein as a guide.

(6) R. Paul and G. Anderson, *J. Am. Chem. Soc.*, **82**, 4596 (1960).

Acknowledgment.—We thank the National Science Foundation for fellowships to R. D. and for generous financial support under an N.S.F. grant (G-14473). A grant (RG-6966) from the National Institutes of Health provided additional assistance.

Experimental

Bis-(8-quinolyl) Carbonate.—To *ca.* 100 ml. of liquid phosgene contained in a 2-l. three-necked flask cooled in ice and equipped with a Dry Ice condenser and addition funnel was rapidly added with magnetic stirring a solution of 75 g. of 8-quinolol in one liter of methylene chloride. After the addition was completed the reaction mixture was stirred for 5 minutes, then filtered under nitrogen pressure. The yellow precipitate so obtained was washed with methylene chloride, then stored over potassium hydroxide in a vacuum desiccator overnight to remove residual solvent and phosgene. This yellow material, presumably a mixture of hydrochlorides of 8-quinolyl and bis-(8-quinolyl) carbonate, was shaken in a separatory funnel with 800 ml. of methylene chloride and a solution of 45 g. of potassium carbonate in 900 ml. of water until both layers were nearly colorless. The methylene chloride layer was drawn off and evaporated to dryness under reduced pressure. The residue was recrystallized from ethyl acetate to give 45.3 g. (56%) of product, m.p. 181°, infrared absorption at 5.62μ (in CH_2Cl_2). The analytical sample was recrystallized to constant melting point from ethyl acetate; m.p. 183.5–184.0°.

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.14; H, 3.82; N, 8.86. Found: C, 72.33; H, 3.78; N, 8.84.

Carbo-(8-quinoloxy)-D,L-phenylalanine.—A solution of 0.165 g. (1.0 mmole) of D,L-phenylalanine, 0.316 g. (1.0 mmole) of bis-(8-quinolyl) carbonate and 0.14 ml. (1.0 mmole) of triethylamine in 15 ml. of tetrahydrofuran and 8 ml. of water was allowed to stand at room temperature for 3 hr. The organic solvent was removed from the reaction mixture by evaporation at reduced pressure. The aqueous suspension so obtained was acidified with excess acetic acid and cooled to 0°. The precipitated solid was collected by filtration and recrystallized from acetonitrile to give 0.111 g. (33%) of product, m.p. 289–290°. The analytical sample obtained by further recrystallization of the product from acetonitrile had the same melting point.

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.91; H, 4.86; N, 8.17.

Carbobenzoxy-D,L-phenylalanine Cyclohexylamide.—To a stirred suspension of 4.23 g. (16.7 mmoles) of N-ethyl-5-phenylisoxazolium 3'-sulfonate[7] in 45 ml. of acetonitrile was added a solution of 5.00 g. (16.7 mmoles) of carbobenzoxy-D,L-phenylalanine and 1.68 g. (16.7 mmoles) of triethylamine in 35 ml. of acetonitrile and the mixture was stirred at 0° for one hour. A solution of 1.67 g. (16.7 mmoles) of cyclohexylamine in 10 ml. of acetonitrile was added to the reaction mixture and the resulting solution was stirred at room temperature overnight. The precipitated product was collected by filtration, washed with a small amount of acetonitrile, and air-dried, giving 5.36 g. of crude product, m.p. 159–160°. Clayton, Kenner and Sheppard give a melting point of 165° for the L-compound.[8]

D,L-Phenylalaninecyclohexylamide.—The synthesis of this compound was carried out in the manner described in the literature for the L-compound.[8] The analytical sample was recrystallized to constant melting point from ligroin; m.p. 78–79°. The literature melting point for the L-compound is 101–102°.

Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.39; H, 8.90; N, 11.21.

The tosylate salt was prepared by mixing equimolar quantities of D,L-phenylalaninecyclohexylamide and *p*-toluenesulfonic acid in acetone, followed by dilution of the solution so formed with ether and cooling in the freezer. The precipitated salt was collected by filtration, m.p. 233–235°. The analytical sample was recrystallized to constant melting point from ethylene glycol dimethyl ether; m.p. 234–235°.

(7) R. B. Woodward, R. A. Olofson and H. Mayer, *ibid.*, **83**, 1010 (1961).

(8) D. W. Clayton, G. W. Kenner and R. C. Sheppard, *J. Chem. Soc.*, 371 (1956).

Anal. Calcd. for $C_{22}H_{30}N_2O_4S$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.30; H, 7.49; N, 6.58.

Carbo-(8-quinoloxy)-D,L-phenylalaninecyclohexylamide. A.—A solution of 0.387 g. (1.57 mmoles) of D,L-phenylalaninecyclohexylamide and 0.500 g. (1.57 mmoles) of bis-(8-quinolyl) carbonate in 16 ml. of methylene chloride was kept at 0° overnight. The solution was evaporated to dryness under reduced pressure. The residue was triturated with ether and collected by filtration. The solid product was washed with much ether and air-dried to give 0.54 g. (82%), m.p. 155–157°. The analytical sample was recrystallized to constant melting point from benzene; m.p. 155–156°, infrared band at 5.72 and 6.0 μ (CH_2Cl_2).

Anal. Calcd. for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.07. Found: C, 71.65; H, 6.60; N, 9.90.

B.—To a magnetically stirred suspension of 0.250 g. (0.988 mmole) of N-ethyl-5-phenylisoxazolium 3′-sulfonate[7] in 5 ml. of acetonitrile was added 0.332 g. (0.988 mmole) of carbo-(8-quinoloxy)-D,L-phenylalanine and 0.14 ml. (1.0 mmole) of triethylamine. The reaction mixture was stirred at 0° for 1 hour, then 0.12 ml. (0.988 mmole) of cyclohexylamine was added and the reaction was stirred at 0° overnight. The precipitate which formed was collected by filtration giving 0.370 g. of product (91%), m.p. 151–153°, having proper infrared spectrum.

Hydrolysis of Carbo-(8-quinoloxy)-D,L-phenylalaninecyclohexylamide.—A solution of 0.259 g. (0.621 mmole) of carbo-(8-quinoloxy)-D,L-phenylalaninecyclohexylamide and 0.126 g. (0.311 mmole) of cupric tosylate in 20 ml. of tetrahydrofuran and 20 ml. of water was allowed to stand for 1 hour at room temperature. The reaction mixture was concentrated to half its volume under reduced pressure and filtered. The filtrate was treated with excess hydrogen sulfide and the suspension of cupric sulfide so formed was filtered through Celite. The latter filtrate was evaporated to dryness under reduced pressure. The residue was triturated with acetone and collected by filtration to give 0.199 g. (77%) of D,L-phenylalaninecyclohexylamide tosylate, m.p. 233–235°.

Hydrolysis of Carbo-(8-quinoloxy)-aniline.[9]—A solution of 0.50 g. (1.9 mmoles) of carbo-(8-quinoloxy)-aniline and 0.77 g. (1.9 mmoles) of cupric tosylate in 30 ml. of tetrahydrofuran and 30 ml. of water was allowed to stand at room temperature for 72 hr. The reaction mixture was concentrated to half its volume under reduced pressure, diluted with 30 ml. of water, and filtered. The filtrate was treated with excess hydrogen sulfide and the suspension of cupric sulfide so formed was filtered through Celite. The latter filtrate was lyophylyzed and the residue was crystallized from acetone–ether to give 0.31 g. (60%) of anilinium tosylate, m.p. 219–227°.

Glycinanilide Dihydrate.—A solution of 5 g. (0.03 mole) of α-isonitrosoacetanilide[10] in 250 ml. of methanol was hydrogenated using 0.5 g. of 10% palladium-on-charcoal as catalyst at an initial pressure of 60 p.s.i. in a Parr apparatus until hydrogen uptake ceased (30 min.). In this time 109% of the theoretical amount of hydrogen was taken up. The reaction mixture was filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was taken up in 50 ml. of hot water. The resulting solution was decolorized with charcoal and filtered while hot. The filtrate was kept at 0° overnight and the precipitated product was collected by filtration and air-dried, giving 4.5 g. (80%), m.p. 59–60°; literature[11] value 61–62°.

The tosylate salt was prepared by mixing glycinanilide dihydrate and *p*-toluenesulfonic acid in acetone solution and collecting the solid product by filtration. The analytical sample was recrystallized to constant melting point from ethanol–ether; m.p. 222.0–222.5°, infrared absorption 5.9 μ (KBr).

Anal. Calcd. for $C_{15}H_{19}N_2O_4S$: C, 55.70; H, 5.92; N, 8.66. Found: C, 55.96; H, 5.71; N, 8.50.

Carbo-(8-quinoloxy)-glycinanilide.—A solution of 10.6 g. of bis-(8-quinolyl) carbonate and 5.0 g. of glycinanilide dihydrate in 330 ml. of methylene chloride was kept at 0° for 48 hr. The precipitate formed was collected by filtration, giving 7.2 g. of material, m.p. 115–118°. This crude product was purified by precipitation from acetone solution with water, giving 6.2 g. (72%) of product, m.p. 131–133°. The analytical sample was recrystallized to constant melting point from ethyl acetate; m.p. 136.0–136.5°, infrared bands at 5.75 and 5.9 μ (KBr).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.05; H, 4.66; N, 12.89.

Hydrolysis of Carbo-(8-quinoloxy)-glycinanilide. A. With Cupric Acetate.—A solution of 0.228 g. (0.712 mmole) of carbo-(8-quinoloxy)-glycinanilide and 3.85 ml. of 0.1 *M* cupric acetate solution in 25 ml. of acetone and 21 ml. of water was allowed to stand at room temperature for 0.5 hr. The reaction mixture was evaporated to half its volume under reduced pressure, diluted with 25 ml. of water, and filtered. The filtrate was treated with excess hydrogen sulfide and the suspension of cupric sulfide so formed was filtered through Celite. The latter filtrate was evaporated to dryness under vacuum to give 0.116 g. (92.5%) of 3-phenylhydantoin, m.p. 153–156°. Material recrystallized to constant melting point from water had m.p. 157–158°, literature[12,13] m.p. 159°; infrared bands at 5.60 and 5.75μ (CH_2Cl_2).

B. With Cupric Tosylate.—The method used in all the experiments with this catalyst is shown by the following example. A solution of 0.229 g. (0.714 mmole) of carbo-(8-quinoloxy)-glycinanilide and 0.145 g. (0.357 mmole) of cupric tosylate in 24 ml. of ethylene glycol dimethyl ether and 24 ml. of distilled water was allowed to stand at room temperature for 1 hour. The reaction mixture was concentrated to half its volume under reduced pressure, diluted with 20 ml. of water and filtered. The filtrate was treated with excess hydrogen sulfide and the suspension of cupric sulfide so formed was filtered through Celite. The latter filtrate was continuously extracted with 200 ml. of methylene chloride for 6 hr. The layers were separated, and the aqueous layer was evaporated to dryness under reduced pressure. The residue was triturated with acetone and collected by filtration to give 0.0957 g. (41.8%) of glycinanilide tosylate, m.p. 221–222°. The methylene chloride extract was washed with 25-ml. portions of 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution, and dried over sodium sulfate. The dry extract was evaporated to dryness under reduced pressure to give 0.0486 g. (38.5%) of 3-phenylhydantoin identified by its infrared spectrum.

C. With Nickel Tosylate.—A solution of 0.1944 g. (0.606 mmole) of carbo-(8-quinoloxy)-glycinanilide and 0.122 g. (0.303 mmole) of nickel tosylate in 20 ml. of water and 20 ml. of acetone was allowed to stand at room temperature for 3 days. The reaction mixture was concentrated to half its volume under reduced pressure, diluted with 20 ml. of water, and filtered. The filtrate was treated with an excess of a 5% solution of 8-quinolol in 2 *N* acetic acid and the resulting suspension was filtered. The latter filtrate was worked up using continuous extraction as in the preceding experiment to give 0.1086 g. (55.6%) of glycinanilide tosylate, m.p. 222°, and 0.0377 g. (35.4%) of 3-phenylhydantoin.

D. With Uranyl Tosylate.—A solution of 0.220 g. (0.686 mmole) of carbo-(8-quinoloxy)-glycinanilide and 0.210 g. (0.343 mmole) of uranyl tosylate in 23 ml. of ethylene glycol dimethyl ether and 23 ml. of water was allowed to stand at room temperature for 44 hr. The reaction mixture was evaporated to half its volume under reduced pressure, diluted with 25 ml. of water, and filtered. The filtrate was worked up directly by the extraction method used in the previous experiments to give 0.1131 g. (51.3%) of glycinanilide tosylate, m.p. 219–221°, and 0.0389 g. (32.2%) of 3-phenylhydantoin.

E. With Ferrous Tosylate.—A solution of the reactants made up as usual was allowed to stand at room temperature for 4 days. The reaction was worked up as in the nickel tosylate hydrolysis to give 0.0704 g. (72.2%) of 3-phenylhydantoin and 0.0807 g. of a white solid, m.p. 227–246°, which could not be freed of ferrous tosylate.

F. Other Conditions.—A number of runs was made with cupric tosylate in 50% aqueous mixture with the following solvents: acetone, ethylene glycol dimethyl ether, aceto-

(9) M. T. Leffler and E. J. Matson, *J. Am. Chem. Soc.*, **70**, 3439 (1948).

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nitrile and tetrahydrofuran. All gave a mixture of glycine anilide and the hydantoin; the former product appeared to be slightly favored by the order given above. Decreasing the relative amount of water lead to a sharp increase in the relative amount of hydantoin. Use of sodium acetate, triethylamine or toluenesulfonic acid as catalyst in 50% aqueous diglyme gave hydantoin as the only product.

Carbo-(8-quinoloxy)-imidazole.—A solution of 3.40 g. of N,N′-carbonyldiimidazole[6] and 1.45 g. of 8-quinolol in 20 ml. of anhydrous tetrahydrofuran was allowed to stand at room temperature for 3 hr. The reaction mixture was poured with stirring into 200 ml. of water and the precipitate so formed collected by filtration and dried under vacuum to give 1.60 g. (67%) of carbo-(8-quinoloxy)-imidazole, m.p. 136–140°. The analytical sample was recrystallized to constant melting point from benzene; m.p. 136–137°, infrared band at 5.61 μ (CH_2Cl_2).

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.14; H, 3.68; N, 17.91.

Bis-N,N′-(2-acetanilidyl)-urea.—A solution of 0.150 g. of glycinanilide dihydrate and 0.119 g. of carbo-(8-quinoloxy)-imidazole in 10 ml. of methylene chloride was allowed to stand at room temperature for 2 hr. The precipitated material was collected by filtration to give 0.079 g. (61%) of bis-N,N′-(2-acetanilidyl)-urea, m.p. 256–258°. This material was recrystallized to constant melting point from dimethylformamide–water; m.p. 265.8–266.0°.

Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.56; H, 5.56; N, 17.17. Found: C, 62.41; H, 5.54; N, 17.27.

The filtrate was evaporated under reduced pressure. The residue was triturated with ether and collected by filtration to give 0.028 g. of material m.p. 118–119°, which was shown to be impure 3-phenylhydantoin by its infrared spectrum, yield 20%.

Reaction of Carbo-(8-quinoloxy)-glycinanilide with Glycinanilide Dihydrate.—A mixture of 0.321 g. of carbo-(8-quinoloxy)-glycinanilide, 0.186 g. of glycinanilide dihydrate and 10 ml. of methylene chloride was stirred at room temperature for 4 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was taken up in 20 ml. of boiling acetone. The acetone-insoluble material was collected by filtration to give 0.0484 g. (15%) of bis-N,N′-(2-acetanilidyl)-urea, m.p. 267–268°. The acetone solution was diluted with an equal volume of water and kept at 0° overnight. The precipitated material was collected by filtration to give 0.222 g. (69%) of carbo-(8-quinoloxy)-glycinanilide, m.p. 136–137°. To the filtrate was added *ca.* 200 mg. of *p*-toluenesulfonic acid, and the resulting solution was continuously extracted with methylene chloride for 10 hr. The aqueous layer was evaporated to dryness under reduced pressure. The residue was triturated with acetone and collected by filtration to give 0.170 g. (53%) of glycinanilide tosylate, m.p. 228–229°. The methylene chloride solution was washed with 1 *N* hydrochloric acid and saturated sodium bicarbonate solution, then evaporated to dryness under reduced pressure, leaving 0.0303 g. (17%) of 3-phenylhydantoin identified by its infrared spectrum.

Carbo-(8-quinoloxy)-glycine Ethyl Ester.—To a suspension of 1.40 g. (10 mmoles) of glycine ethyl ester hydrochloride in 125 ml. of chloroform was added 3.15 g. (10 mmoles) of barium hydroxide and a few drops of water,[14] and the mixture was swirled until all the hydrochloride had gone into solution. This mixture was dried over barium oxide and filtered. To the filtrate was added 3.16 g. (10 mmoles) of bis-(8-quinolyl) carbonate and the resulting mixture was refluxed for 2 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from carbon tetrachloride to give 2.56 g. (94%) of product, m.p. 128–135°. The analytical sample was recrystallized to constant melting point from carbon tetrachloride; m.p. 134–135°.

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.28; H, 5.07; N, 10.11.

Hydrolysis of Carbo-(8-quinoloxy)-glycine Ethyl Ester.—A solution of 0.250 g. (0.912 mmole) of carbo-(8-quinoloxy)-glycine ethyl ester and 0.108 g. (0.456 mmole) of nickel chloride hexahydrate in 30 ml. of water and 30 ml. of diethylene glycol dimethyl ether was allowed to stand at room temperature for 4 days. The reaction mixture was evaporated to dryness under reduced pressure and the residue was taken up in water, treated with an excess of a 5% solution of 8-quinolol in 2 *N* acetic acid and filtered. The filtrate was extracted continuously with methylene chloride until the aqueous layer was colorless. The layers were separated and the aqueous layer was evaporated to dryness under reduced pressure to give 0.0739 g. (58%) of glycine ethyl ester hydrochloride, m.p. 139–141°, having an infrared spectrum identical with that of the commercially available material.

N-Benzyl-2-chloroacetamide.[15]—To a magnetically stirred suspension of 12.9 g. of anhydrous potassium carbonate in a solution of 10 g. of benzylamine in 75 ml. of dry acetone was added dropwise 20 g. of chloroacetyl chloride. After the addition was completed, the mixture was stirred and refluxed for 15 min., cooled, and poured into 100 ml. of 2 *N* hydrochloric acid. The precipitated product was collected by filtration, washed with water and air-dried, giving 15.3 g. (88%) of material, m.p. 89°. After one recrystallization from ether the product melted at 92°. The literature[15] melting point is 93°.

2-Amino-N-benzylacetamide.[16]—A solution of 12.1 g. of N-benzyl-2-chloroacetamide and 40 g. of anhydrous ammonia in 300 ml. of 95% ethanol was allowed to stand at room temperature for 5 days in a tightly stoppered flask. The solution was evaporated to dryness under reduced pressure and the residue was taken up in 100 ml. of distilled water. The aqueous solution was passed through a column of 150 g. of Dowex-3 ion exchange resin in the free base form. The column was then washed with de-ionized water until the eluent was neutral. The total basic eluent was lyophilized to give 7.0 g. (65%) of white powder, m.p. 57°. A Beilstein test showed the presence of traces of halogen in the product. The analytical sample was twice sublimed at 110° at 0.3 mm., m.p. 50°. The literature[16] value is 46–49°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37. Found: C, 65.60; H, 7.36.

The tosylate salt was prepared by mixing acetone solutions of the free amine and *p*-toluenesulfonic acid and collecting the precipitated product by filtration. The analytical sample was recrystallized to constant melting point from ethanol–ether; m.p. 253–254°.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.11; H, 6.02; N, 8.21.

Carbo-(8-quinoloxy)-glycinebenzylamide Hydrate.—A solution of 0.83 g. (5 mmoles) of 2-amino-N-benzylacetamide and 1.58 g. (5 mmoles) of bis-(8-quinolyl)-carbonate in 50 ml. of methylene chloride was kept at 0° for 5 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was taken up in 10 ml. of methylene chloride. The methylene chloride solution was diluted with 40 ml. of ether and kept at 0° overnight. The solid product was collected by filtration giving 1.58 g. (90%) of product, m.p. 87–90°. In some runs a product was obtained, m.p. 107–108°, which presumably was the anhydrous amide, but this material gave the hydrated form at once on recrystallization from aqueous acetone, or gradually on repeated crystallization from methylene chloride–ether. The analytical sample was recrystallized to constant melting point from methylene chloride–ether; m.p. 91–92°.

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.48; H, 5.62; N, 11.69.

Hydrolysis of Carbo-(8-quinoloxy)-glycinebenzylamide Hydrate. A. With Cupric Tosylate.—A solution of 0.273 g. (0.774 mmole) of carbo-(8-quinoloxy)-glycinebenzylamide hydrate and 0.157 g. (0.387 mmole) of cupric tosylate in 26 ml. of ethylene glycol dimethyl ether and 26 ml. of water was allowed to stand for 1 hour at room temperature. The reaction was worked up as in the corresponding hydrolysis of carbo-(8-quinoloxy)-glycinanilide to give 0.2439 g. of material, m.p. 238–239°. On recrystallization from ethanol this material gave 0.1888 g. (73%) of glycinebenzylamidetosylate, m.p. 250–251°.

B. With Nickel Tosylate.—A solution of 0.220 g. (0.622 mmole) of carbo-(8-quinoloxy)-glycine benzylamide hy-

(14) The presence of water is necessary for the successful utilization of the method of F. W. Foreman, *Biochem. J.*, **13**, 378 (1919); personal communication from Mr. C. P. Lillya of these laboratories.

(15) E. Hofstetter and A. E. Wilder Smith, *Helv. Chim. Acta*, **36**, 1698 (1953).

(16) J. Brunken and G. Bach, *Ber.*, **89**, 1363 (1956).

drate and 0.125 g. (0.311 mmole) of nickel tosylate in 21 ml. of ethylene glycol dimethyl ether and 21 ml. of water was allowed to stand for 40 hr. at room temperature. The reaction was worked up as in the corresponding hydrolysis of carbo-(8-quinoloxy)-glycinanilide to give 0.1612 g. (77%) of glycinebenzylamide tosylate, m.p. 259–260°.

Carbobenzoxyglycylglycinebenzylamide.—To a stirred suspension of 2.53 g. of N-ethyl-5-phenylisoxazolium 3′-sulfonate[7] in 45 ml. of acetonitrile was added 2.09 g. of carbobenzoxyglycine and 1.01 g. of triethylamine and the resulting mixture was stirred for 1 hour at 0°. To the reaction mixture was then added a suspension of 2-amino-N-benzylacetamide in 50 ml. of acetonitrile and stirring was continued at the same temperature overnight. The reaction mixture was filtered to give 3.20 g. of material, m.p. 173–175°. The filtrate was evaporated to dryness under reduced pressure. The residue was taken up in saturated sodium bicarbonate solution and the insoluble material collected by filtration, washed with water and air-dried to give 0.80 g., m.p. 156–160°. The combined precipitates were recrystallized from 95% ethanol to give 3.30 g. (89%) of product, m.p. 161–162°. Further recrystallization from the same solvent did not change the melting point.

Anal. Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.33; H, 5.92; N, 12.20.

Glycylglycine Benzylamide Hydrobromide.—A mixture of 2.6 g. of carbobenzoxyglycylglycinebenzylamide and 9 ml. of a 4 *N* solution of hydrogen bromide in acetic acid was heated for 5 min. on a steam-bath. The reaction mixture was diluted with ether and the solid material collected by filtration. The solid was washed with much ether and air-dried to give 2.27 g. of material, m.p. 205–208°. This material was recrystallized from ethanol–ether to give 1.74 g. (79%) of glycylglycinebenzylamide hydrobromide, m.p. 222–223°. Further recrystallization from the same solvent gave no further change in the melting point.

Anal. Calcd. for $C_{11}H_{16}BrN_3O_2$: C, 43.72; H, 5.34; N, 13.91. Found: C, 44.09; H, 5.23; N, 14.18.

Carbo-(8-quinoloxy)-glycylglycinebenzylamide.—To a suspension of 0.318 g. (1.0 mmole) of glycylglycine benzylamide hydrobromide in 3 ml. of methanol was added 0.544 ml. (1.0 mmole) of a 1.84 *N* solution of sodium methoxide in methanol and the mixture was swirled until a clear solution was obtained. The methanol solution was evaporated to dryness under reduced pressure. The residue was taken up in 10 ml. of methylene chloride and the resulting suspension was filtered. To the filtrate was added 0.316 g. (1.0 mmole) of bis-(8-quinolyl) carbonate and the resulting solution was kept at 0° for 8 hr. The reaction mixture was evaporated to dryness under reduced pressure. The residue was triturated with several portions of ether and the solid material obtained was collected by filtration to give 0.360 g. (92%) of product, m.p. 130–132°. The analytical sample was recrystallized to constant melting point from 2-butanone–ether; m.p. 132–133°.

Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 63.91; H, 4.97; N, 14.16.

Glycylglycinebenzylamide Tosylate.—A solution of 0.201 g. (0.512 mmole) of carbo-(8-quinoloxy)-glycylglycinebenzylamide and 0.104 g. (0.256 mmole) of cupric tosylate in 17 ml. of acetone and 17 ml. of water was allowed to stand at room temperature for 0.5 hr. The reaction was worked up as in the hydrolysis of carbo-(8-quinoloxy)-D,L-phenylalaninecyclohexylamide to give 0.139 g. (69%) of glycylglycinebenzylamide tosylate, m.p. 236–237°. The analytical sample was recrystallized to constant melting point from ethanol–ether; m.p. 238–239°.

Anal. Calcd. for $C_{18}H_{23}N_3O_5S$: C, 54.95; H, 5.89; N, 10.68. Found: C, 55.07; H, 5.74; N, 10.78.

[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Acylation by a Metal-ion Salt–Quinone System

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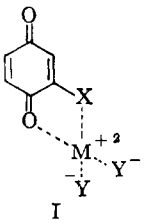
Metal-ion salts, *e.g.*, carboxylates, are converted to the corresponding anhydrides (or esters in the presence of an alcohol) by interaction with the coördinating quinone 6,7-dichloro-5,8-quinolinequinone (II, DQQ). The quinone is simultaneously transformed into the complexed 6-oxy-7-chloro-5,8-quinolinequinone anion. The properties of the metal salt–DQQ combination are detailed as is the evidence concerning chemical mechanisms.

Intensification of the electrophilic character of an organic grouping by coördination with a metal cation is fundamental to many cases of catalysis by such ions, including Friedel–Crafts syntheses, the Meerwein–Ponndorf–Oppenauer processes and certain hydrolytic reactions.[2–4] The electron-withdrawing capacity of metal ions also accounts for their function as catalysts through stabilization of negative charge.[5] Superimposed on the simple electron-withdrawing effect is the extremely favorable entropy factor in cases of stable chelate ring formation,[6–8] a matter of enormous importance in the area of biochemistry.[9] The present paper concerns an investigation of the effect of metal cation coördination on an already electron-deficient quinonoid system of the type I with X a coördinating



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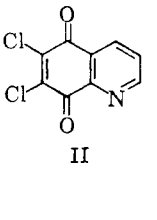

II

group in the quinone molecule, M a divalent chelating metal ion and Y^- an appropriate anion. At the outset it was anticipated that in a complex such as I the quinonoid moiety would be electron deficient relative to the uncoördinated condition with the result that its reactions with nucleophiles would be accelerated both at oxygen and at carbon. Such complexes might be potent hydride acceptors, for

(1) Research Associate under a grant (G-14473) from the National Science Foundation.

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