are formed. These reactions are currently being investigated.

EXPERIMENTAL

All spectra were obtained using a Beckman IR-4 spectrophotometer, sodium chloride optics. Band frequencies were checked against known frequencies of polystyrene (film). As solids or saturated solutions of samples were used to obtain the spectra, the bands were classified according to an arbitrary intensity scale (in per cent absorption): 10–15, very, very weak (vvw); 15–20, very weak (vw); 20–80, medium (m); 80–90, strong (s); and above 90, very strong (vs). Spectra of the crystalline solids were obtained using the standard potassium bromide disc techniques using two different concentrations of sample. The above intensities refer to a concentration of about 1 mmole/g. of potassium bromide. The solution spectra were obtained using chloroform as the solvent. Solutions were made at room temperature and excess sample removed by filtration.

Ammonolysis of 2-benzoyl-4-benzyl-5-amino-3-isoxazolone XI; *R = benzyl.* (a) *With ammonia.* The benzoyl derivative (1.0 g.) was heated on the steam bath with concentrated ammonium hydroxide solution (10 ml.) until a solution was obtained. Extraction of the hot solution with chloroform (2–15-ml. portions) afforded benzamide, (0.17 g.) which crystallized from water, m.p. and mixed m.p. 127°. Acidification of the aqueous layer with dilute hydrochloric acid yielded the parent compound, (VII; R = benzyl) (0.28 g., 43%), m.p. and mixed m.p. 147°.

(*b*) *With benzylamine.* Similarly, this benzoyl derivative (730 mg.) was heated first at 50° for 20 min., then at 90° for 5 min. with an aqueous solution of benzylamine (0.27 g. in 12 ml.). On cooling a solid separated which was extracted with boiling benzene (25 ml.). The benzene-insoluble material (60 mg.) proved to be starting material. Crystallization of the benzene extract afforded 200 mg. of the parent compound (VII; R = benzyl). Concentration of the benzene filtrate and dilution with petroleum ether, (b.p. 30–60°; 7 ml.) yielded *N*-benzylbenzamide, (325 mg., 67%) m.p. and mixed m.p. 103–105°. Acidification of the aqueous layer with dilute hydrochloric acid afforded an additional 175 mg. of the parent compound (total of 375 mg. represents 87% recovery), m.p. and mixed m.p., 145–147°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

Reissert Compound Studies. II. Nature of the Quinoline[1, 2]

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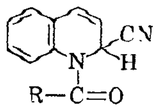
Reaction of a wide variety of 3-, 4-, 5-, 6-, and 7-substituted quinolines with benzoyl chloride and potassium cyanide in methylene chloride–water has resulted in the formation of the appropriate Reissert compounds. The yields of Reissert compounds were largest when the substituents were electron-donating groups. No Reissert compounds could be obtained from 2- and 8-substituted quinolines. With one exception all the Reissert compounds gave benzaldehyde on acid-catalyzed hydrolysis.

Reissert compounds[4] (I and II) result from the addition of an acyl and a cyano group to quinolines and isoquinolines. Initial interest in Reissert compounds arose from the fact that their acid-catalyzed hydrolysis yielded aldehydes, thus providing a general method for the preparation of aldehydes from acid chlorides.[4] More recent interest, however, has been in the use of Reissert compounds in the synthesis of various heterocyclic compounds.[4,5]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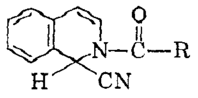
II

If Reissert compounds are to be useful reagents for further synthesis, the effect of substituents on the quinoline base must be understood. A survey of the literature has revealed that more than half of the quinolines subjected to this reaction have failed to yield Reissert compounds. In addition to quinoline[6] itself, 6-methoxy-,[7] 7-methoxy-,[8] 6-chloro-,[9] 6-methyl-,[9] and 5,6-benzoquinoline[10] have been shown to yield Reissert compounds. On the other hand when the substituent is the 5-nitro,[7] 5-amino,[7] 5-acetamido,[7] 6-dimethylamino,[7] 6-nitro,[9] 7-nitro,[7] 8-hydroxy,[7] 8-methoxy,[7] 8-nitro,[9] 8-benzoyloxy,[7] 8-acetoxy,[7] or 2-methyl[7] group, the reaction fails. These results seem to point out an obvious steric effect resulting from a substituent in the 2- or 8- position of the quinoline ring, but

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[1] Part I, F. D. Popp and W. Blount, *Chem. & Ind.* (*London*), 550 (1961).

[2] Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 1961. A preliminary report was also presented at the Meeting-in-Miniature of the Florida Section of the ACS, Hollywood Beach, Fla., May 1961. This work was supported in part by a grant from the Research Corp.

[3] The major portion of this work has been abstracted from the M.S. thesis of W. B.

[4] W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

[5] See L. R. Walters, E. G. Podrebarac, and W. E. McEwen, *J. Org. Chem.*, **26**, 1161 (1961) and references cited therein to earlier work of McEwen and co-workers.

[6] A. Reissert, *Ber.*, **38**, 1603 (1905).

[7] A. Gassman and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

[8] E. Spath and O. Brunner, *Ber.*, **57**, 1234 (1924).

[9] I. W. Elliott, Jr., *J. Am. Chem. Soc.*, **77**, 4409 (1955).

[10] Footnote in M. Colonna and S. Fatutta, *Gazz. chim. ital.*, **83**, 622 (1953).

it is not possible to generalize on the electronic effects that result in a favorable reaction.

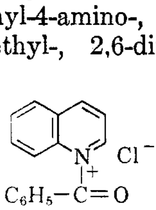
In an attempt to gather more information regarding the effect of substituents on the quinoline base ten additional quinolines were caused to react with benzoyl chloride and potassium cyanide using the common aqueous method.[4] Of these bases, only 6-bromo-, 7-methyl-, and 3-acetamidoquinoline gave Reissert compounds. Obviously the reaction of further quinolines using the aqueous method could not be expected to clarify the situation.

The aqueous method of Reissert compound formation suffers from the disadvantage that both the starting quinoline and the product are insoluble in water. It was thought that the oily, messy reaction mixtures thus obtained might be a factor which explains why many quinolines, for no apparent reasons, do not form Reissert compounds. The other general method available for Reissert compound formation is the nonaqueous benzene–hydrogen cyanide method.[11] This method has the obvious disadvantages associated with the use of hydrogen cyanide. In addition one half of the quinoline is tied up as the salt which could be a disadvantage where the quinoline was available only in small quantities. Other solvent systems such as acetonitrile, benzonitrile, ether, dioxane, chloroform, and acetone have been tried[12] without success. Use of liquid sulfur dioxide[12] or dimethylformamide-water[9] gave inconsistent results. We have now found that the use of methylene chloride–water is a good solvent system with general utility in the preparation of Reissert compounds.[1]

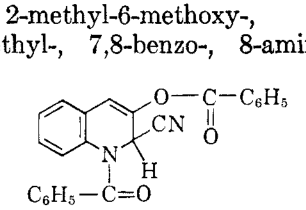
Although the methylene chloride–water system is still heterogeneous it has the advantage that all the reactants and products are soluble in one phase or the other. Also water is slightly soluble in methylene chloride. This solubility is apparently the deciding factor since, with the exception of 2- and 8-substituted quinolines, a wide variety of quinolines have been found to give Reissert compounds with this solvent system. In fact Reissert compounds have been prepared from 3-, 4-, 5-, 6-, and 7-substituted quinolines and from disubstituted quinolines. A number of quinolines having various types of substituents in these positions, including all those previously reported as not giving Reissert compounds, gave positive results in this study.[13]

The results are summarized in Table I. The yields of Reissert compounds with substituents in each position varied with the electronic character of the substituent, quinolines with electron-donating groups generally giving the highest yields and those with electron-withdrawing groups the lowest yields. This can be rationalized in two ways. An increased electron density in the quinoline would increase it reactivity towards the benzoyl chloride in the formation of III, and once III was formed the positive charge could be shared by positions 2, 4, 5, and 7 of the quinoline. An electron-donating group in these positions would thus stabilize III.

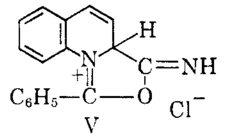
By use of this solvent system the following quinolines failed to yield any Reissert compounds: 2-methyl-, 2-chloro-, 2-methyl-4-hydroxy-, 2-methyl-4-amino-, 2-methyl-6-methoxy-, 2,4-dimethyl-, 2,6-dimethyl-, 7,8-benzo-, 8-amino-, 8-nitro-, 8-chloro-, 8-hydroxy-, and 8-methylquinoline.



III



IV



V

With the exception of the Reissert compound from 3-hydroxyquinoline all the Reissert compounds yielded benzaldehyde on acid-catalyzed hydrolysis.[14,15] The proximity of the carbonyl function in the 3-position of the Reissert compound IV[16] to the cyano group may interfere with the interaction of the cyano group and the carbonyl function in the 1-position which is necessary for the formation of V (or its tautomers). The presence of a benzoylamino group in the 3-position of the Reissert compound lead to only a 46% yield of benzaldehyde on acid-catalyzed hydrolysis and this might be explained in the same manner. In the case of the 3-acetamido compound, however, an 89% yield of benzaldehyde was obtained. It is possible that the decrease in bulk offered by the methyl group allowed the amide function to be out of the proximity of the cyano group. With only two other general exceptions the yields of benzaldehyde were quite high. The nitro substituted Reissert compounds such as those from 5-, 6-, and 7-nitroquinoline and from 5-nitrosoquinoline[17] gave very low yields of benzaldehyde on acid-catalyzed

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[11] J. M. Groscheintz and H. O. L. Fisher, *J. Am. Chem. Soc.*, **63**, 2021 (1941).

[12] R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1626 (1940).

[13] 5-Acetamidoquinoline did not give a Reissert compound as a crystalline material using this method. An oil was obtained (78% yield on the assumption that this was pure Reissert compound). On acid-catalyzed hydrolysis of this oil a 55% yield of benzaldehyde was obtained, as its 2,4-dinitrophenylhydrazone, indicating that a Reissert compound had been formed but could not be crystallized.

[14] W. E. McEwen, R. H. Terss, and I. W. Elliott, *J. Am. Chem. Soc.*, **74**, 3605 (1952).

[15] R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

[16] All Reissert compounds from hydroxy- and aminoquinolines were obtained as the benzoylated products.

[17] F. D. Popp and W. Blount, unpublished observations.

TABLE I

QUINOLINE REISSERT COMPOUNDS

R	M.P.[b]	Yield, % Method A[c]	Yield, % Method B[d]	Calcd. C	Calcd. H	Calcd. N	Found[a] C	Found[a] H	Found[a] N	Yield, % Benzaldehyde[e]
3-Acetamido-	160–161[f]	50	15	71.90	4.76		71.90	4.54		89
3-Amino-[g]	169–170[h]	68	0			11.08			10.84	46
3-Bromo-	125[f]	15	0	60.20	3.27		60.25	3.27		93
3-Hydroxy[i]	179–180[j]	58		75.78	4.24		75.61	4.30		0
4-Methyl-	173–175[k,h]	71	Trace							87
4-Hydroxy-[i]	157–158[h]	98	0	75.78	4.24	7.37	75.49	4.38	7.10	86
4-Chloro-	141[f]	33		69.28	3.76		69.39	3.94		92
4-Methoxy-	146[f]	82		74.47	4.86		74.53	4.86		86
5-Amino-[g]	187–188[h]	63	0	75.97	4.52	11.08	75.83	4.57	11.31	99
5-Nitro-	162–163[l]	19		66.88	3.63		66.85	3.86		10
5-Hydroxy-[i]	172–173[j]	99		75.78	4.24		75.85	4.56		99
5-Carbomethoxy-	116–117[m]	61		71.69	4.43		71.72	4.42		93
6-Methyl-	144[f,n]	99	52							90
6-Bromo-	165–166[f]	48	40	60.20	3.27		59.95	3.15		93
6-Amino-[g]	195[h]	95		75.97	4.52		75.77	4.80		96
6-Methoxy-	126 [o,f]	89	88							95
6-Nitro-	200–201[p]	29	0	66.88	3.63		66.89	3.71		43
6-Hydroxy-[i]	188[h]	99		75.78	4.24		75.87	4.23		75
6-Dimethylamino-	176[f]	59	0	75.22	5.65	13.85	75.04	5.77	13.73	93
6-Carbomethoxy-	115[j]	49		71.69	4.43		71.58	4.54		99
7-Methyl-	164–165[f]	64	54	78.81	5.14		79.11	5.29		84
7-Hydroxy-[i]	126–127[f]	89		75.78	4.24		76.05	4.33		99
7-Nitro-	185[f]	17		66.88	3.63		66.70	3.58		16
4,6-Dimethyl-	130–131[h]	94	0	79.14	5.59		78.88	5.70		—[q]
4-Hydroxy-7-chloro-[i]	171–172[j]	20		69.49	3.64		69.12	3.61		20
4,7-Dichloro-	155[j]	34	0			8.51			8.26	77
4-Chloro-6-methoxy-	167–168[h]	87		66.57	4.03		66.53	4.03		48
5,6-Benzo-	182[f,r]	94	43	81.27	4.55		81.06	4.61		84

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [b] Melting points are uncorrected. [c] Methylene chloride–water method, see Experimental. [d] Aqueous method, see Experimental. [e] From acid-catalyzed hydrolysis, isolated as the 2,4-dinitrophenylhydrazone, see ref. 14. [f] Recrystallized from 95% ethanol. [g] Compounds from aminoquinolines were isolated as the benzoylamino derivative. [h] Recrystallized from glacial acetic acid. [i] Compounds from hydroxyquinolines were isolated as the benzoate derivative. [j] Recrystallized from 80% acetic acid. [k] Identical with authentic sample, m.p. 174–175°, supplied by Dr. I. W. Elliott, Fisk University. [l] Recrystallized from 75% ethanol. [m] Recrystallized from isopropyl alcohol. [n] Reported m.p. 142–143°, ref. 9. [o] Reported m.p. 127°, ref. 7. [p] Recrystallized from ethyl acetate. [q] Gave positive test for benzaldehyde, quantitative test not made. [r] Previously prepared but no physical constants given, see ref. 10.

hydrolysis. The other cases of low yields of benzaldehyde were in the Reissert compounds from disubstituted quinolines. No apparent explanation is available for these cases.

EXPERIMENTAL

Reagents. Reagent grade benzoyl chloride, methylene chloride, and potassium cyanide were used. The quinolines were obtained commercially or prepared by standard literature procedures.

Aqueous method of Reissert compound formation.[4] To a solution of potassium cyanide (0.048 mole) in 25 ml. of water was added the quinoline (0.016 mole). Benzoyl chloride (0.032 mole) was added dropwise over a period of 2 hr. with vigorous stirring. After an additional 2 hr. of stirring, the solid or oil was collected and washed with water, 10% hydrochloric acid, water, and a small amount of ether. The material was then recrystallized from an appropriate solvent.

Methylene chloride–water method of Reissert compound formation.[1] Benzoyl chloride (0.032 mole) was added over 2 hr. to a stirred mixture of the quinoline (0.016 mole) in 20 ml. of methylene chloride and the potassium cyanide (0.048 mole) in 8 ml. of water. After an additional 6- to 8 hr. of stirring the layers were separated and the water layer washed with 10 ml. of methylene chloride. The combined methylene chloride was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide, and water. The dried (magnesium sulfate) methylene chloride solution was slowly evaporated to give the Reissert compound. If an oil was obtained at this point, it could be crystallized by treatment with the appropriate solvent. The material was then recrystallized from an appropriate solvent as indicated in Table I.

Acid-catalyzed hydrolysis of Reissert compounds.[14] Concentrated hydrochloric acid (11 ml./0.5 g. of Reissert compound) was added to an equimolar mixture of Reissert compound and 2,4-dinitrophenylhydrazine, and the mixture was heated for 30 min. After the mixture had been allowed to stand at room temperature for 2 days, the quantity of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 239°, was determined.

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