2,3,3-Tribromo-2-methylbutane (8). The preparation of **8** was accomplished using a modification of a reported procedure.[28] Bromine (1.07 g) was added dropwise to a stirred, ice-cooled solution of 3-bromo-3-methyl-2-butene (1.00 g) in carbon tetrachloride (10 ml). The solution was then allowed to warm to room temperature and the solvent was removed under aspirator pressure. The resulting solid residue was recrystallized from ethanol to give white crystals which sublime before melting (1.30 g, 64.5%). The nmr (CCl_4) showed δ 2.73 (3 H, s), 2.09 (6 H, s).

2,2,3,3-Tetrachlorobutane (9). Chlorine was bubbled slowly into a stirred, cooled (ice bath) solution of dimethylacetylene (0.59 g) in carbon tetrachloride (10 ml) for 3 hr. The solvent was removed under aspirator pressure and the solid residue recrystallized from ethanol. The material was purified by glpc (3.05 m × 0.95 cm 10% poly-*m*-phenyl ether on 60–80 Chromosorb W at 100° with 200 ml/min of He). The nmr in CCl_4 showed δ 2.42 (s) with no other peaks. **Caution!** Violent reaction may occur after several minutes if chlorine accumulates. Preparation on a large scale should be avoided.

2,2,3,3-Tetrabromobutane (10). Bromine (3.2 g) was added dropwise to a stirred, ice-cooled solution of dimethylacetylene (0.59 g) in pentane (10 ml). After the addition was complete, the ice bath was removed and stirring was continued for 30 min. The solvent was removed under aspirator pressure and the residue recrystallized from ethanol: mp 246–248° (s); reported[29] mp 243°. The nmr (CCl_4) showed δ 2.87 (s), no other peaks. The ir (CCl_4) showed no double-bond absorption.

(28) J. Schmidt and F. Leipprand, *Chem. Ber.*, 37, 548 (1909).

(29) J. Wislicenus and P. Schmidt, *Ann.*, 313, 225 (1900).

1,3-Dipolar Addition Reactions of Reissert Compounds

William E. McEwen,* Isidore C. Mineo, and Yvonne H. Shen

Contribution from the Department of Chemistry of the University of Massachusetts, Amherst, Massachusetts 01002. *Received October 19, 1970*

Abstract: The mesoionic intermediate, **2**, produced by loss of fluoroboric acid from 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**) is essentially a munchnone imine. As such, it can undergo 1,3-dipolar addition reactions with suitable dipolarophiles. The reaction of **1** with ethyl phenylpropiolate was especially significant in that both the bridged intermediate, 2-carbethoxy-1,3-diphenyl-3-hydroxy-13-cyano-3,13-dihydrobenzpyrrocoline-3,13-lactim (**3**), and the aromatic heterocyclic compound, ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**6**), were isolated. The formation of a bridged intermediate such as **3** had been postulated to occur in the various 1,3-dipolar addition reactions of sydnones, sydnone imines, and munchnones; however, this type of structure had always remained a theoretical concept only, since the elimination of carbon dioxide or isocyanic acid to form the final aromatic heterocyclic product had occurred rapidly. The bridged adduct **3** was found to undergo thermolysis at a high temperature to give **6** plus a polymer of isocyanic acid. The proof of structure of **6** consisted of its hydrolysis and decarboxylation to give 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**10**). In an independent synthesis, 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**11**) was prepared by the condensation of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with cinnamonitrile. Hydrolysis of the amide and decarboxylation of the resulting acid gave **10**. Reaction of **1** with dimethyl acetylenedicarboxylate gave dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**). The structure of **8** was established in two different ways. First of all, the ester was subjected to hydrolysis and the resulting acid to decarboxylation to give 3-phenylpyrrolo[2,1-*a*]isoquinoline (**17**), which was also obtained by cyclodehydration of β-(1-isoquinolyl)propiophenone (**18**) in polyphosphoric acid. In the second proof of structure, dimethyl 2-(1-isoquinolyl)-3-benzoylmaleate (**19**) was prepared by the reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with dimethyl acetylenedicarboxylate. Treatment of **19** with 100% phosphoric acid gave **8**.

A mechanism for the acid-catalyzed hydrolysis of a Reissert compound (a 1-acyl-1,2-dihydroquinaldonitrile or a 2-acyl-1,2-dihydroisoquinaldonitrile) has been proposed[1] in which a mesoionic compound is postulated to be an intermediate. Since such a mesoionic intermediate is essentially a munchnone imine, and since munchnones, sydnones, and sydnone imines are known to undergo 1,3-dipolar addition reactions readily,[2] it was anticipated that a 1,3-dipolarophile might be used to capture the intermediate. This expectation was realized, as described below.[3]

When 2-benzoyl-1,2-dihydroisoquinaldonitrile was treated with fluoroboric acid in glacial acetic acid, a yellow precipitate (**1**) of the Reissert salt was obtained. The reactions of **1** with ethyl phenylpropiolate, ethyl tetrolate, and dimethyl acetylenedicarboxylate were examined. Exceptionally promising results were obtained in the case of the reaction with ethyl phenylpropiolate; the anticipated, initial, bridged intermediate **3** could actually be isolated as a moderately stable, crystalline compound. This appears to be the first example of the isolation of such an intermediate among all of the known 1,3-dipolar addition reactions of the same general type involving munchnones, sydnones, and sydnone imines.

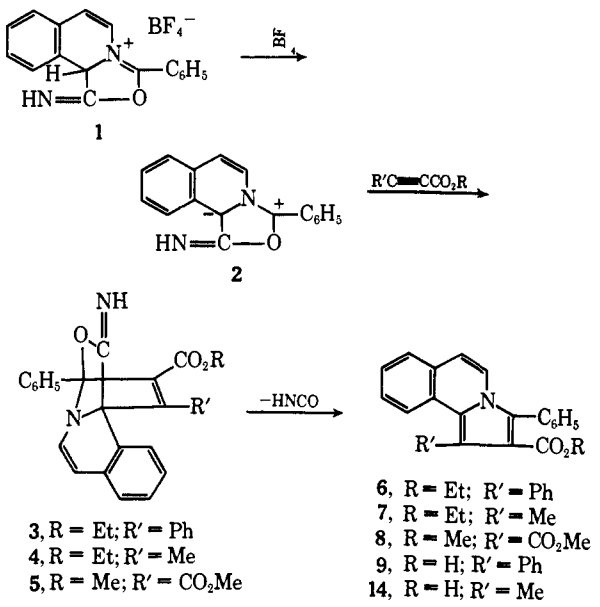
Two colorless compounds of molecular formulas $C_{28}H_{22}N_2O_3$ (**3**) and $C_{27}H_{21}NO_2$ (**6**), respectively, were obtained by the reaction of **1** with ethyl phenylpropiolate in boiling methylene chloride–ethanol solution.

(1) (a) R. L. Cobb and W. E. McEwen, *J. Amer. Chem. Soc.*, 77, 5042 (1955); (b) E. K. Evanguelidou and W. E. McEwen, *J. Org. Chem.*, 31, 4110 (1966), and papers cited therein.

(2) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 2, 565 (1963); (b) R. Huisgen, H. Gotthardt, H. Bayer, and F. Schaefer, *ibid.*, 3, 136 (1964).

(3) A preliminary account of a small portion of this work has been published: W. E. McEwen, I. C. Mineo, Y. H. Shen, and G. Y. Han, *Tetrahedron Lett.*, 5157 (1968).

Compound **3** showed an NH absorption peak (3440 cm^{-1}), a carbonyl peak (1740 cm^{-1}), and an imino peak (1695 cm^{-1}) in its infrared absorption spectrum. The nmr spectrum showed a 2 H triplet at δ 0.75, a 3 H quartet at δ 3.82, a 16 H multiplet at δ 7.3–8.6, and the characteristic NH broad peak (1 H) at δ 8.95. The elemental analyses were also consistent with the structure of 2-carbethoxy-1,3-diphenyl-3-hydroxy-13-cyano-3,13-dihydrobenzpyrrocoline-3,13-lactim (**3**). The other compound, **6**, showed a carbonyl absorption peak (1690 cm^{-1}) and characteristic pyrrolo ring absorption peaks (1200–1100 cm^{-1}) in its infrared spectrum. The nmr spectrum showed a 2 H triplet at δ 0.78, a 3 H quartet at δ 3.9, and a 16 H multiplet at δ 6.8–7.8. This compound, **6**, not only lacked an NH absorption peak in its infrared spectrum, but the elemental analyses also indicated that it differed from **3** by having one unit less of HNCO. The structure ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**6**) was assigned on the basis of these data and the degradative and synthetic studies to be described later.



3, R = Et; R′ = Ph
4, R = Et; R′ = Me
5, R = Me; R′ = CO_2Me

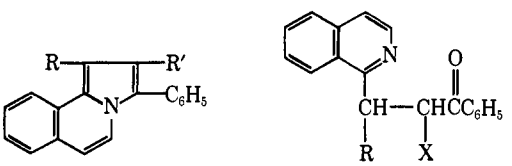
6, R = Et; R′ = Ph
7, R = Et; R′ = Me
8, R = Me; R′ = CO_2Me
9, R = H; R′ = Ph
14, R = H; R′ = Me

Even though the adduct **3** undergoes conversion to **6** at a much slower rate than do the similar non-isolable adducts derived from munchnones, sydnones, and sydnone imines, it is nevertheless obvious that the conversion does occur slowly, even in refluxing methylene chloride–ethanol solution. Therefore, it was felt that both **6** and a product derived from isocyanic acid could be isolated by pyrolysis of pure **3**. Indeed, when **3** was heated at 220–230° for 30 min, **6** was obtained in 65% yield by chromatography of the pyrolysate. Furthermore, when **3** was pyrolyzed in a sublimator, a white, porcelain-like solid collected on the cold finger. This compound proved to be insoluble in water, ether, chloroform, weak acids, and weak bases. It melted above 300°, and its infrared spectrum showed the presence of an imino peak at 1700 cm^{-1}. These physical and chemical properties are the same as those described[4] and expected for a polymer of isocyanic acid.

(4) (a) A. Hantzsch, *Ber.*, **38**, 1013 (1905); (b) T. L. Davis and K. C. Blanchard, *J. Amer. Chem. Soc.*, **51**, 1806 (1929).

The proof of structure of **6**, and thus of the orientation of reagents in the formation of the adduct **3**, consisted of saponification and subsequent decarboxylation of **6** to give 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**10**), which was also synthesized by two independent and unambiguous methods. One independent synthesis consisted of the condensation of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with cinnamonitrile to give 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**11**),[5] with subsequent removal of the carboxamide group by the action of hot 100% phosphoric acid.

The starting point for the second independent synthesis of **10** consisted of the reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with ethyl cinnamate to give α-carbethoxy-β-(1-isoquinolyl)-β-phenylpropiophenone (**12**).[6] Hydrolysis and decarboxylation of **12** afforded β-(1-isoquinolyl)-β-phenylpropiophenone (**13**), which was cyclized to **10** by the action of 100% phosphoric acid.



10, R = Ph; R′ = H
11, R = Ph; R′ = $CONH_2$
15, R = Me; R′ = H
16, R = Me; R′ = $CONH_2$
17, R = R′ = H

12, R = Ph; X = CO_2Et
13, R = Ph; X = H
18, R = X = H

The question of whether the condensation of the mesoionic intermediate **2** with ethyl phenylpropiolate to give **3** entails the synchronous formation of the new covalent bonds or whether one bond is formed at a time with intervention of a zwitterionic intermediate is the subject of the accompanying article.[7]

An attempt was made to learn more about factors influencing orientation in the condensation of **2** with dipolarophiles. Specifically, ethyl tetrolate was employed in place of ethyl phenylpropiolate in a typical 1,3-dipolar addition reaction. The steric requirements of a methyl group are less than those of a phenyl group, and it was deemed possible that two different adducts might be formed in the ethyl tetrolate reaction. An intractable gum was obtained when **1** was treated with ethyl tetrolate in refluxing methylene chloride–ethanol solution. In view of the indications that polymerization of ethyl tetrolate had also taken place, the gum was saponified by the use of potassium hydroxide in ethanol solution. Appropriate work-up of the reaction mixture gave a carboxylic acid which was eventually shown to be 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**14**). Thus, although no product corresponding to **4** could be isolated, the orientation in the ethyl tetrolate reaction was the same as that in the ethyl phenylpropiolate reaction.

(5) Boekelheide and Godfrey had previously prepared 3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide by the condensation of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with acrylonitrile: V. Boekelheide and J. C. Godfrey, *ibid.*, **75**, 3679 (1953).

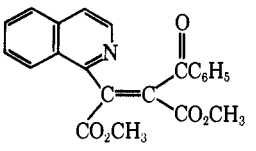
(6) Boekelheide and Godfrey[5] had carried out a similar condensation reaction with ethyl acrylate.

(7) W. E. McEwen, K. D. Kanitkar, and W. M. Hung, *ibid.*, **93**, 4484 (1971).

The proof of structure of **14** paralleled that used for the proof of structure of **6**. Decarboxylation of **14** gave 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline (**15**); reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with crotononitrile afforded 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**16**), which was converted to **15** by the action of 100% phosphoric acid.

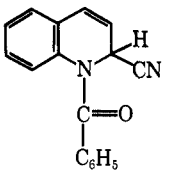
Attempts to carry out the condensation of **1** with dimethyl acetylenedicarboxylate were successful, as expected, since the latter compound is a highly reactive 1,3-dipolarophile.[2b,8] Dimethyl 3-phenylpyrrolo[2,1-*a*]-isoquinoline-1,2-dicarboxylate (**8**) was obtained in 90% yield by reaction of **1** with dimethyl acetylenedicarboxylate in refluxing methylene chloride–ethanol solution, but no product corresponding to **5** could be isolated. The same product, **8**, was also obtained when dimethylformamide–ethanol was used as the solvent. The compound exhibited two carbonyl peaks (1710 and 1725 cm^{-1}), the characteristic fused pyrrolo ring absorption peaks (1160–1270 cm^{-1}), and two sets of C–H absorption peaks (2940 and 2995–3070 cm^{-1}) in its infrared spectrum. Its nmr spectrum showed two singlets at δ 3.73 (3 H) and 4.04 (3 H) and a multiplet at δ 6.65–7.70 (11 H).

The structure of the product, **8**, was confirmed in two different ways. First of all, it was subjected to hydrolysis and the resulting acid to decarboxylation to give 3-phenylpyrrolo[2,1-*a*]isoquinoline (**17**). The latter compound was also prepared by cyclodehydration of β-(1-isoquinolyl)propiophenone (**18**) by the action of polyphosphoric acid. In the second proof of structure, dimethyl 2-(1-isoquinolyl)-3-benzoylmaleate (**19**) was prepared by the reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with dimethyl acetylenedicarboxylate. Treatment of **19** with 100% phosphoric acid at 120° gave dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**), identical in every regard with the product of the 1,3-dipolar addition reaction.



19

Reactions of quinoline Reissert compounds with 1,3-dipolarophiles proved to be less satisfactory than those of the isoquinoline Reissert compounds. The reaction of 1-benzoyl-1,2-dihydroquinaldonitrile (**20**) hydrochloride with dimethyl acetylenedicarboxylate in methylene chloride–ethanol solution, for example, gave dimethyl 1-phenylpyrrolo[2,1-*a*]quinoline-2,3-dicarboxylate (**21**) in only 7% yield. The yield was increased to 10% by the use of dimethylformamide as the solvent. The proof of structure of **21** is described elsewhere.[3,9]



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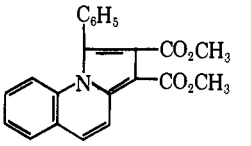

21

Experimental Section

The melting points recorded are uncorrected and each has been taken on a modified Hershberg melting point apparatus. The infrared spectra have been recorded on a Beckman Model IR 10 infrared spectrophotometer. The nuclear magnetic resonance spectra have all been recorded on a Varian Associates Model A-60 spectrometer at a sweep width of 1000 cps. Column adsorption chromatography has been effected on a 3 × 30 cm column of activated alumina (Merck No. 71707) with chloroform–benzene (1:1) as the eluting solvent for all pyrrolo[2,1-*a*]isoquinolines, except as otherwise indicated. Qualitative thin layer chromatography has been conducted for each new reaction product on a microscope slide prepared with silica gel "C" (according to Stahl) from Brinkmann Instruments Inc. Iodine vapor was used as the visualizing agent. Solvents, with the exception of 95% ethanol, have been suitably purified, dried, and stored over molecular sieves (Linde type 5A). Analyses were carried out by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (1). To 10.0 g of 2-benzoyl-1,2-dihydroisoquinaldonitrile[10] was added 30 ml of glacial acetic acid, and the mixture was warmed and stirred until all of the Reissert compound had dissolved. Heating was discontinued, and 40 ml of of 48% fluoroboric acid (Fisher Scientific Co.) was added with stirring from a dropping funnel. The solution became orange colored. At the end of 5 min, the reaction mixture was cooled in an ice bath. A bright yellow precipitate appeared and was collected by filtration. The solid was washed with successive small portions of anhydrous ether (100 ml total) until the odor of acetic acid was virtually eliminated. The salt was dried overnight in a desiccator and amounted to 12.2 g (90%), mp 196–198° dec.

Anal. Calcd for $C_{17}H_{13}N_2OBF_4$: C, 58.65; H, 3.76; N, 8.05; B, 3.11; F, 21.83. Found: C, 58.90; H, 3.85; N, 8.20; B, 3.19; F, 21.57.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (1) with Ethyl Phenylpropiolate. A suspension of 5.9 of **1** in 50 ml of methylene chloride was heated to boiling, and to the stirred mixture was added dropwise 8.5 ml of ethyl phenylpropiolate. After the mixture had been refluxed for 10 min, 50 ml of 95% ethanol was slowly introduced, and the still heterogeneous mixture was refluxed for an additional 20 min. The methylene chloride was gradually removed by distillation, and a deep orange solution remained. This was cooled and filtered to remove a porcelain-like material (a polymer of isocyanic acid) which had formed. Evaporation of the filtrate *in vacuo* left a gummy residue (A), which was dissolved in 100 ml of benzene and subjected to chromatography on neutral alumina. a 1:1 mixture of benzene and chloroform being used as the eluent. The product obtained from the first yellow band gave, upon crystallization from 95% ethanol, 2.9 g (44%) of ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**6**), mp 101–102°.

Anal. Calcd for $C_{27}H_{21}NO_2$: C, 82.84; H, 5.41; N, 3.58. Found: C, 82.85; H, 5.50; N, 3.71.

In order to obtain seed crystals of 2-carbethoxy-1,3-diphenyl-3-hydroxy-13-cyano-3,13-dihydrobenzpyrrocoline-3,13-lactim (**3**), the gummy residue (A) from a second experiment identical with the one described above was subjected to decolorization by the action of Norite in a 95% ethanol solution. After evaporation of a small portion of the alcohol solution, the light yellow gummy residue was stirred for 4 hr with Skelly B solvent. The gum solidified and the solid was collected by filtration and powdered. This powder was used to seed the main portion of the alcohol solution. There was obtained 1.2 g of crude, crystalline **3**.

Once seed crystals of **3** had been obtained, it could also be isolated from the original reaction mixture by chromatography. The second yellow band from the original chromatographic separation of A

(8) (a) R. Huisgen and H. Gotthardt, *Chem. Ber.*, 839, 1059 (1968); (b) R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, 829 (1968); (c) R. Benson, W. Linn, and O. Webster, *J. Amer. Chem. Soc.*, 87, 3651 (1965).

(9) G. Fun-Huei Yang Han, Ph.D. Dissertation, University of Massachusetts, 1969.

(10) J. Weinstock and V. Boekelheide, *Org. Syn.*, **38**, 58 (1958).

contained a mixture of **3** and **6**, but more of the former than the latter; compound **3**, mp 217–218° dec, crystallized when the eluent of this band was concentrated and seeded with **3**. It was difficult to obtain a completely pure sample of **3** owing to its tendency to decompose to **6** and $(HCNO)_x$, even on recrystallization.

Anal. Calcd for $C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45. Found: C, 76.74; H, 5.10; N, 6.46.

1,3-Diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic Acid (9). A solution of 5.0 g of **6** and 0.75 g of potassium hydroxide in 70 ml of 95% ethanol was refluxed overnight. The color of the solution changed from colorless to light yellow and a considerable amount of precipitate formed. Hydrochloric acid (5% solution) was added to neutralized the solution. The precipitate was found to be soluble in the neutralized solution. Several portions of benzene were used to extract the final mixture. The combined benzene solution was evaporated to dryness. The residue, when recrystallized twice from 95% ethanol, gave 3.3 g (71%) of colorless 1,3-diphenypyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**9**), mp 214–215.5° with decarboxylation.

Anal. Calcd for $C_{25}H_{17}NO_2$: C, 82.62; H, 4.72; N, 3.85. Found: C, 82.48; H, 4.72; N, 4.00.

1,3-Diphenylpyrrolo[2,1-*a*]isoquinoline (10). In a manner similar to the procedure described by Buckles and Wheeler,[11] 1.0 g (0.00275 mol) of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**9**), 3.76 ml of quinoline, and 0.05 g of copper chromite were mixed and stirred. The reaction mixture was heated by means of an oil bath until the temperature reached 210–220°. The temperature was kept within this range for 80 min. The solution was then cooled immediately, and 127 ml of 10% hydrochloric acid was added to dissolve the quinoline. The desired product was then extracted from the mixture with five 100-ml portions of ether. The combined organic ether solution was filtered three times to remove small particles of catalyst, then it was washed with small portions of 10% sodium carbonate solution and finally the ether removed by distillation. The residue was dissolved in 95% ethanol, which gave 0.8 g (0.0025 mol) of crystalline 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**10**), mp 136–138°. The yield was 91%.

Anal. Calcd for $C_{24}H_{17}N$: C, 90.25; H, 5.37; N, 4.39. Found: C, 90.16; H, 5.43; N, 4.40.

1,3-Diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (11). A solution of 30.0 g (0.116 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 400 ml of anhydrous dioxane and 200 ml of anhydrous ether was cooled to −10° with stirring, and 70 ml of phenyllithium (2.14 *M* in ether and benzene, 0.150 mol) solution[12] was introduced from the dropping funnel, the mixture being maintained in a nitrogen atmosphere. A dark red solution resulted, and a solution of 20.0 g (0.155 mol) of cinnamonitrile in 50 ml of anhydrous ether was then added to the mixture. The deep red color faded after the mixture had been stirred overnight. Dry Ice (200 g) and water (200 ml) were added to the resulting mixture, which led to the separation of two layers. The aqueous layer was extracted with ether and combined with the organic layer which was deep orange in color. Removal of solvent by evaporation in a rotary evaporator and dissolution of the residue in a small amount of chloroform with subsequent addition of 95% ethanol gave 24.7 g of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**11**), mp 225–227°. It was obtained in the form of bright orange prisms. On concentration of the mother liquor, there was obtained 5.7 g of the starting material and an additional 4.0 g of the product. The total yield was 70%.

Anal. Calcd for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.72. Found: C, 82.54; H, 5.12; N, 7.90.

Conversion of 11 to 10. A mixture of 2 g (0.0055 mol) of pulverized 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**11**) and 50 ml of 100% phosphoric acid was stirred and heated in an oil bath until the temperature rose to 120°, whereupon the solid dissolved and the solution became dark brown. At 140–160°, gas evolution began and sublimation of a colorless compound to the upper portion of the flask could be seen. The temperature was maintained in this range for 2 hr, then the mixture was cooled to room temperature and 100 ml of ice–water was added. After the mixture had been made basic by the addition of sodium hydroxide solution, the aqueous solution was extracted several times with ether. The combined ether solution (about 300 ml) was evaporated and the residue dissolved in 1 ml of chloroform. Ethanol was added gradually to this solution and a crystalline product was obtained. The weight of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**10**) was 1.2 g (69%). Its mp was 136–137.5°. A mixture melting point test of this compound with that obtained from the decarboxylation of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**9**) showed no depression, and the infrared spectra of the two samples were superimposable.

α-Carbethoxy-9-(1-isoquinolyl)-9-phenylpropiophenone (12). A mixture of 30.0 g (0.116 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile, 400 ml of anhydrous dioxane, and 200 ml of anhydrous ether was cooled to −10°, and 70 ml of a freshly prepared solution of phenyllithium (0.15 mol) in ether and benzene was introduced in a dropwise manner into the stirred mixture. The solution immediately developed a deep red color, which is characteristic of the lithium salt of the Reissert compound. A solution of 21 ml of ethyl cinnamate in 70 ml of dioxane was added slowly to the mixture. Although the deep red color of the mixture had disappeared by the time that the addition was completed, the mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was then decomposed by the addition of 400 ml of water and enough solid carbon dioxide to make the aqueous layer faintly acidic. Two layers separated. After removal of the organic layer, the aqueous solution was extracted three times with 100-ml portions of ether. Concentration of the combined extracts gave a dark residue, which, upon crystallization from 95% ethanol, gave 28 g (60%) of a colorless solid, α-carbethoxy-β-(1-isoquinolyl)-β-phenylpropiophenone (**12**), mp 120–122°.

Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.67; N, 3.42. Found: C, 79.60; H, 5.67; N, 3.52.

β-(1-Isoquinolyl)-9-phenylpropiophenone (13). A solution of 4.0 g (0.01 mol) of α-carbethoxy-β-(1-isoquinolyl)-β-phenylpropiophenone (**12**) and 0.6 g of potassium hydroxide in 50 ml of 95% ethanol was refluxed for 10 hr. A yellow suspension appeared at the termination of this period. The solvent was removed by rotary evaporation. Dilute hydrochloric acid was added in a amount sufficient to make the solution neutral. The aqueous solution was extracted with benzene, and the benzene solution (about 200 ml) was then washed with water and sodium bicarbonate solution. Evaporation of the benzene and crystallization of the residue from 95% ethanol gave 2.4 g of colorless prisms of **13**, mp 104–106°.

Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.13; H, 5.52; N, 4.19.

Cyclization of 13. A suspension of 0.32 g (0.00095 mol) of β-phenyl-β-(1-isoquinolyl)propiophenone (**13**) in 5.0 ml of 100% phosphoric acid was stirred and heated in an oil bath until the temperature of the reaction mixture reached 120°. It was maintained at this temperature for 30 min and then allowed to cool to room temperature. After it had been neutralized with sodium hydroxide solution, the mixture was extracted with three 100-ml portions of ether. Evaporation of the ether left an orange residue which was dissolved in 5.0 ml of chloroform. Enough 95% ethanol was added to the solution to induce crystallization of the solute; 0.27 g (90%) of the product, mp 139–141°, was obtained.

A mixture melting point test of this sample of **10** with that obtained by the decarboxylation of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**9**) showed no depression, and the infrared spectra of the two samples were superimposable.

Nmr Spectra of 12 and 13. The nmr spectrum of **12** showed a triplet at δ 0.94, a quartet at 3.95, a multiplet at 7.1–8.5, and a singlet (2 H) at 6.06. From these results, it was reasoned that **12** exists as a mixture of keto–enol tautomers, and this was confirmed by the observation of a positive ferric chloride test. The fact that the same chemical shift was observed for the benzilic proton and the proton of the enolic hydroxyl group was merely a coincidence. The nmr spectrum of **13** showed sets of multiplets at δ 7.1–8.5, a quartet (1 H) at δ 5.84, another quartet (1 H) at δ 4.84, and still another quartet (1 H) at δ 3.53. The β-carbon of the propiophenone moiety of **13** is asymmetric, which causes the two α-protons to exist in different magnetic environments; this is the reason for the complicated chemical shifts. A positive ferric chloride test was also observed for **13**.

Triphenyl(acetylcarbethoxymethylene)phosphorane. A mixture of 104.8 g (0.4 mol) of triphenylphosphine and 1120 ml of anhydrous benzene was stirred and cooled in an ice bath while 184.4 ml of a carbon tetrachloride solution of chlorine (28.4 g of chlorine, 0.4 mol) was added from a dropping funnel. The addition was carried out as rapidly as possible consistent with the exothermic reaction being kept under control. After the addition had been completed, the dropping funnel was replaced quickly by one that contained a solution of 128 ml (96 g, 0.96 mol) of triethylamine in 300 ml of

(11) R. E. Buckles and N. G. Wheeler, *Org. Syn.*, **33**, 88 (1953).

(12) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 931.

anhydrous benzene. The amine solution was added to the milky white mixture during a period of 30 min with stirring. Finally, 52 g (0.4 mol) of ethyl acetoacetate was added slowly, and the solution became yellowish. The cooling bath was removed and sufficient heat was applied for 10–15 min to maintain the temperature at 80°. The orange mixture was filtered after it had been cooled to room temperature. Concentration of the filtrate was effected at reduced pressure, and the residual solution was subjected to column chromatography on activated alumina, benzene being used as the solvent. Cyclohexane was added to the eluent, which had been concentrated, until it became cloudy, and then just enough benzene was added to render the solution clear again. The ylide crystallized in the form of large prisms. Recrystallization of this material from a mixture of benzene and cyclohexane gave 110 g (70%) of triphenyl(acetylcarbethoxymethylene)phosphorane, mp 168–169°.

Anal. Calcd for $C_{24}H_{23}O_3P$: C, 73.83; H, 5.94; P, 7.93. Found: C, 73.67; H, 6.03; P, 8.01.

Ethyl Tetrolate. The pyrolysis of 110 g of triphenyl(acetylcarbethoxymethylene)phosphorane was carried out for 1 hr at 265° (5 mm) with magnetic stirring. The phosphorane first became liquid and the color turned brown. Some of the phosphorane sublimed to the upper part of the flask and condenser. At and above 260° (5 mm), ethyl tetrolate started to distill, the distillate being collected in a receiver cooled in a Dry Ice–acetone bath. Redistillation of the impure acetylenic compound under atmospheric pressure gave 22 g (69%) of ethyl tetrolate, bp 162–165° in agreement with literature.[13]

Ethyl tetrolate was also prepared in 86% yield by the reaction of sodium propyne with ethyl chloroformate in ethyl ether.

Reaction of 1 with Ethyl Tetrolate. A mixture of 3.5 g of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**), 3 ml of ethyl tetrolate, and 50 ml of methylene chloride was brought to reflux, and 75 ml of 95% ethanol was introduced. After having been refluxed overnight, the mixture still remained heterogeneous, and the color had become orange. The mixture was cooled, evaporated to dryness, and finally extracted with 200 ml of benzene. The benzene solution was subjected to column chromatography on neutral alumina. The eluent, after evaporation, gave an orange gummy residue. This same reaction was repeated many times until the amount of gummy residue collected was 10 g. This was chromatographed on neutral alumina, benzene–chloroform being used as the solvent, but no crystalline material could be obtained from the eluent fractions.

A solution of 5.0 g of potassium hydroxide in 50 ml of 95% ethanol was added to the gummy residue. After the solution had been refluxed for 2 hr, the mixture was evaporated almost to dryness. Dilute hydrochloric acid was added to the residue until the solution was slightly acidic. Benzene (200 ml) was used to extract the acidic solution, and this benzene extract was evaporated. The residue was decolorized with activated charcoal in ethanol solution. Eventually a yellow crystalline compound started to precipitate from the 95% ethanol solution. It proved to be 1-methyl-3-phenylpyrrolo-[2,1-*a*]isoquinoline-2-carboxylic acid (**14**), mp 242–245°.

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.32; H, 5.44; N, 4.47.

1-Methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (16). A solution of 20.0 g of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 400 ml of anhydrous dioxane and 200 ml of anhydrous ether was cooled to −10° in a nitrogen atmosphere while 50 ml of 2.07 *M* phenyllithium was introduced. A dark red solution soon resulted, and a solution of 5.13 g (0.0773 mol) of crotononitrile in 50 ml of anhydrous ether was added. After having been stirred overnight, the mixture was treated with 200 g of Dry Ice and 200 ml of water, which led to the separation of two layers. The aqueous layer was extracted with ether. The combined ether solution was evaporated to dryness, and the residue was dissolved in 95% ethanol. Bright orange colored needles started to precipitate. The melting point of this compound was 145–146°.

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.33. Found: C, 79.85; H, 5.48; N, 9.50.

1-Methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline (15). Treatment of 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**14**) with copper chromite and quinoline in an oil bath, followed by the addition of 10% hydrochloric acid and separation of the product by extraction with ether, gave, upon evaporation of the ether solution, a colorless compound. The mp was 113–115°.

Treatment of 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**16**) with 100% phosphoric acid at the reaction temperature of 120–140° gave, after the usual work-up, colorless flakes of 1-methyl-3-phenylpyrrolo[2,1-*a*]isoquinoline (**15**), mp 113–115°. A mixture melting point test of the two samples obtained by the different routes showed no depression, and the infrared spectra of the two samples were superimposable.

Reaction of 1 with Dimethyl Acetylenedicarboxylate. A mixture of 3.5 g (0.01 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**), 1.5 g (0.01 mol) of dimethyl acetylenedicarboxylate, and 25 ml of methylene chloride was heated to boiling, and 50 ml of ethanol was added. The mixture was heated at a slow boil for 1 hr, resulting in a black solution. The solution was evaporated to dryness on a steam bath under a slow air stream, and the residue was extracted with ether. The ether was poured off and replenished until it acquired no more color. The combined ether washings were evaporated, and the resulting yellow solid was recrystallized from 95% ethanol, yielding 3.3 g of colorless crystals of dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**), mp 102–103°.

Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.54; H, 4.75; N, 3.90. Found: C, 73.31; H, 4.82; N, 3.88.

The use of dimethylformide–95% ethanol (4:3 parts by volume) as the solvent led to the formation of the same product in about the same yield.

Dimethyl 2-(1-Isoquinolyl)-3-benzoylmaleate (19). A solution of 10.4 g (0.04 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 125 ml of anhydrous ether and 75 ml of anhydrous dioxane was stirred and cooled to −10°, and a solution of 0.04 mol of freshly prepared phenyllithium in benzene and ether was added. The mixture became a dark red solution. A solution of 3.76 ml (0.04 mol) of dimethyl acetylenedicarboxylate in 75 ml of anhydrous ether was then introduced in a dropwise manner over a period of 30 min. The deep red color gradually disappeared, and the mixture turned to pale orange in color. After having been maintained at a temperature of −10° for a few minutes, the temperature of the mixture was allowed to rise to room temperature. The mixture was stirred overnight. After 150 ml of water had been added, two layers separated. The aqueous layer was extracted with ether, and the combined ether solution was washed with water. The ether solution was then evaporated to dryness in a rotary evaporator. A brown residue which remained was dissolved in methanol. Two different kinds of crystals formed, and the compounds giving rise to these different crystal forms could best be separated by column chromatography on neutral alumina, benzene–chloroform being used as the solvent.

A colorless solid which weighed 1.5 g was obtained on evaporation of the eluent of the first band. Its mp was 176–178° after crystallization from methanol.

Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.57; N, 3.73. Found: C, 70.60; H, 4.86; N, 3.60.

Evaporation of the eluent from a second band gave a dark red, crystalline material. This seemed to be a compound of relatively high molecular weight and was not investigated further.

Cyclization of 19. A suspension of 3.7 g (0.01 mol) of dimethyl 2-(1-isoquinolyl)-3-benzoylmaleate (**19**) in 15 ml of 100% phosphoric acid was heated in an oil bath until the temperature rose to 120°, and the mixture was maintained at this temperature for 30 min. The brown mixture was then poured onto 100 g of ice and neutralized with sodium hydroxide solution. Several portions of ether were used to extract the mixture, and the combined ether solution (about 400 ml) was evaporated. The yellow residue was dissolved in benzene and subjected to column chromatography on neutral alumina. The eluent, on evaporation, gave a very poor yield of the desired compound, about 0.3 g of dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**) being obtained. Its mp was 101–103°. A mixture melting point test with the sample obtained by condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**) with dimethyl acetylenedicarboxylate showed no depression, and the infrared spectra of the two samples were superimposeable.

Saponification and Partial Decarboxylation of 8. A solution of 3.6 g (0.01 mol) of dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**) in 25 ml of ethanol was added to a solution of 8.0 g of potassium hydroxide in 25 ml of water, and the mixture was refluxed for 1 hr. The ethanol was evaporated on a steam bath under an air stream. The aqueous solution was poured into a slurry of ice and 10% hydrochloric acid. After having been stirred for 10 min with a glass rod, the suspension was suction filtered. The resulting white solid, 3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylic acid, was recrystallized from 75% ethanol, mp 218–219°. The acid weighed 2.8 g, an 89% yield.

(13) F. Feist, *Justus Liebigs Ann. Chem.*, **345**, 100 (1906).

Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.44; H, 4.53; N, 4.88. Found: C, 79.65; H, 4.78; N, 4.75.

Decarboxylation of 3-Phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylic Acid. To 1.0 g of the acid of mp 218–219° was added 3 ml of quinoline freshly distilled from alumina, and 100 mg of copper chromite catalyst. The flask was placed in an oil bath and heated for 0.5 at 220°. The green mixture was poured into a slurry of ice and 10% hydrochloric acid. The mixture was extracted three times with 20 ml portions of methylene chloride. This solution was concentrated under an air stream, and the residual solid was dissolved in ether. The solution was extracted three times with 10-ml portions of 1 *N* sodium hydroxide solution. The ether solution was evaporated, and a few mg of 3-phenylpyrrolo[2,1-*a*]isoquinoline (**17**), mp 98.5–99°, was obtained. The same compound was also obtained in somewhat better yield by pyrolysis of the sodium salt of the acid. A mixture melting point of this material with a sample of authentic **17** prepared from β-(1-isoquinolyl)propiophenone[5,14] (**18**) by the method of Boekelheide and Godfrey[5] showed no depression. Also, the infrared spectra of the two samples were superimposable.

1-Formamido-3-phenylpyrrolo[2,1-*a*]isoquinoline. A mixture of 1.5 g (0.0052 mol) of 3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylic acid, mp 218–219°, and 5 ml of thionyl chloride was refluxed for 2 hr. The excess thionyl chloride was removed by distillation, and the residue was dissolved in methylene chloride. This solution of the acid chloride was added dropwise to 100 ml of ice cold ammonia, specific gravity 0.9, and stirred magnetically for 12 hr at ambient temperature. The resulting deep red amide was collected by suction filtration and recrystallized from ethanol, mp 204–205°. The yield was 1.1 g (73.3%) based on starting acid.

Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.72; H, 4.89; N, 9.79. Found: C, 79.58; H, 5.07; N, 9.59.

Since this was not identical with the sample of 2-formamido-3-phenylpyrrolo[2,1-*a*]isoquinoline, mp 168–169°, prepared by the method of Boekelheide and Godfrey,[5] this constituted evidence that the carboxyl group was located at the 1 position in the acid of mp 218–219°, as indicated above.

Reissert Salts. When 0.003 mol of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**) was treated with 25 ml of cold 1 *N* sodium hydroxide solution, 2-benzoyl-1,2-dihydroisoquinaldonitrile, mp 125–126°, was recovered in greater than 90% yield.

2-*p*-Anisoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate, mp 210–212° dec, was prepared from 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile[15] in the same manner as described for the preparation of **1**.

Acknowledgment. This work was supported by a research grant (CA-06620) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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Mechanism of 1,3-Dipolar Addition of Reissert Salts to Arylpropiolate Esters

William E. McEwen,* Kumud Bhave Kanitkar, and William Mo-wei Hung

Contribution from the Department of Chemistry of the University of Massachusetts, Amherst, Massachusetts 01002. *Received October 19, 1970*

Abstract: The condensation reactions of 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates (**1**) with ethyl phenylpropiolate (**3a**) were carried out in dimethylformamide–ethanol solution. A kinetics investigation was undertaken under conditions which give rise only to the bridged intermediate **4**, and it was established that each reaction is a second- and first-order reversible one. The specific rate constants of these reactions were found to vary only slightly with changes in the substituent on the aroyl group of the Reissert salt. It is of particular significance that the rate of reaction of 2-*p*-anisoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1b**) with **3a** was found to be slower than that of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1a**) with **3a**. The activation parameters for the reaction of **1b** with **3a** were found to be $\Delta H^{\pm} = 16.3$ kcal/mol and $\Delta S^{\pm} = -25$ eu. The condensation reactions of **1a** with methyl *p*-methoxyphenylpropiolate (**3b**) and methyl *p*-nitrophenylpropiolate (**3c**) were carried out in ethanol–methylene chloride solution. These reactions were found to follow simple second-order kinetics and to give compounds of type **5** as the major products. In these reactions, also, there was a relatively small change in the rate of reaction with the change of substituent in the arylpropiolate ester. Furthermore, a substantial change in solvent polarity caused only a relatively small change in rate. In each of the reactions studied, only one of the two possible orientations of reagents leading to **4** and **5**, respectively, was found to be operative. The structures of all of the products were established in an unambiguous manner by spectral, degradative, and synthetic methods. On the basis of all of the criteria cited above, a concerted mechanism which entails essentially a synchronous formation of the two new covalent bonds is favored over a two-step, ionic mechanism for the 1,3-dipolar cycloaddition reactions under discussion.

The accompanying article[1] presents a description of the 1,3-dipolar addition reactions of certain types of munchnone imines (**2**), derived from the hydrofluoroborate salts of Reissert compounds, with ethyl phenylpropiolate (**3a**), ethyl tetrolate, and dimethyl acetylenedicarboxylate. The reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1a**) with ethyl phenylpropiolate (**3a**) was of particular interest in that the initial, bridged intermediate, 2-carbethoxy-1,3-diphenyl-3-hydroxy-13-cyano-1,13-dihydrobenzpyrrocoline-3,13-lactim (**4a**), was isolable. This represented the first example of the isolation of such an intermediate among all of the known 1,3-dipolar addition reactions of the same general type involving munchnones, sydnones, and sydnone imines.[2]

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