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Studies on Tertiary Amine Oxides. LXXX.[1] Reaction of Quinoline 1-Oxide with Phenylacetic Anhydride

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Treatment of quinoline 1-oxide (**1**) with phenylacetic acid and acetic anhydride in boiling benzene for 10 h gave benzaldehyde (**2**), quinoline (**3**), 2-benzylquinoline (**4**), 2-benzoylquinoline (**5**), phenyl-di(2-quinolyl)carbinol (**6**), di(2-quinolyl) ketone (**7**), and *N*-(2-quinolyl)-2-benzylidene-1,2-dihydroquinoline (**8**) in small yields. The reaction of **1** with phenylacetic anhydride in boiling benzene for 10 h afforded 1,3-diphenyl-1-(2-quinolyl)acetone (**9**) and dibenzyl ketone (**10**) together with small amounts of **2**, **3**, and **5**. Further, it was found that phenylacetic anhydride undergoes decarboxylative coupling upon heating with tertiary amines to give **10**. The mechanisms of these reactions are discussed.

Keywords——nucleophilic reaction; oxidative decarboxylation; decarboxylative coupling; benzaldehyde; 2-benzylquinoline; phenyl-di(2-quinolyl)carbinol; *N*-(2-quinolyl)-2-benzylidene-1,2-dihydroquinoline; 1,3-diphenyl-1-(2-quinolyl)acetone; dibenzyl ketone

While the α-pyridone formation from pyridine 1-oxides and hot acetic anhydride is a well-known reaction,[3] it is also well documented that a variety of carboxylic anhydrides undergo oxidative decarboxylation upon heating with pyridine 1-oxide in an inert solvent, giving the corresponding carbonyl compounds as illustrated in Chart 1.[4-6]

On the other hand, we previously showed that quinoline 1-oxide reacted with phenylacetic acid in refluxing acetic anhydride to give several products shown in Chart 1 in small yields; three of these products arose from nucleophilic attack by the benzyl anion formed by decarboxylation of the phenylacetate anion at the 2-position of the 1-acetoxyquinolinium salt.[7]

We have now investigated the reaction of quinoline 1-oxide with phenylacetic anhydride in boiling benzene in order to explore the relative extent of oxidative decarboxylation.

The reaction of quinoline 1-oxide (**1**) with phenylacetic acid and acetic anhydride in benzene was first examined. When a solution of equimolar amounts of **1**, phenylacetic acid and acetic anhydride in benzene was refluxed for 10 h, benzaldehyde (**2**), quinoline (**3**), 2-benzylquinoline[8] (**4**), 2-benzoylquinoline[9] (**5**), phenyl-di(2-quinolyl)carbinol[7] (**6**), di(2-quinolyl)ketone[10] (**7**), and *N*-(2-quinolyl)-2-benzylidene-1,2-dihydroquinoline (**8**) were obtained in small yields (reaction (I) in Chart 2).

Compound **8** showed blue fluorescence when dissolved in an organic solvent. Its analytical values and mass spectrum (MS) were consistent with the molecular formula $C_{25}H_{18}N_2$. The infrared (IR) spectrum exhibited no absorption band attributable to any functional group and the nuclear magnetic resonance (NMR) spectrum showed signals only in the aromatic region.

Treatment of **8** with hot 60% sulfuric acid or with 3% hydrogen peroxide in acetic acid resulted in almost quantitative recovery of **8**, but quinaldic acid 1-oxide[7] was isolated in 36.4% yield upon heating with 30% hydrogen peroxide in acetic acid. Further, it was found

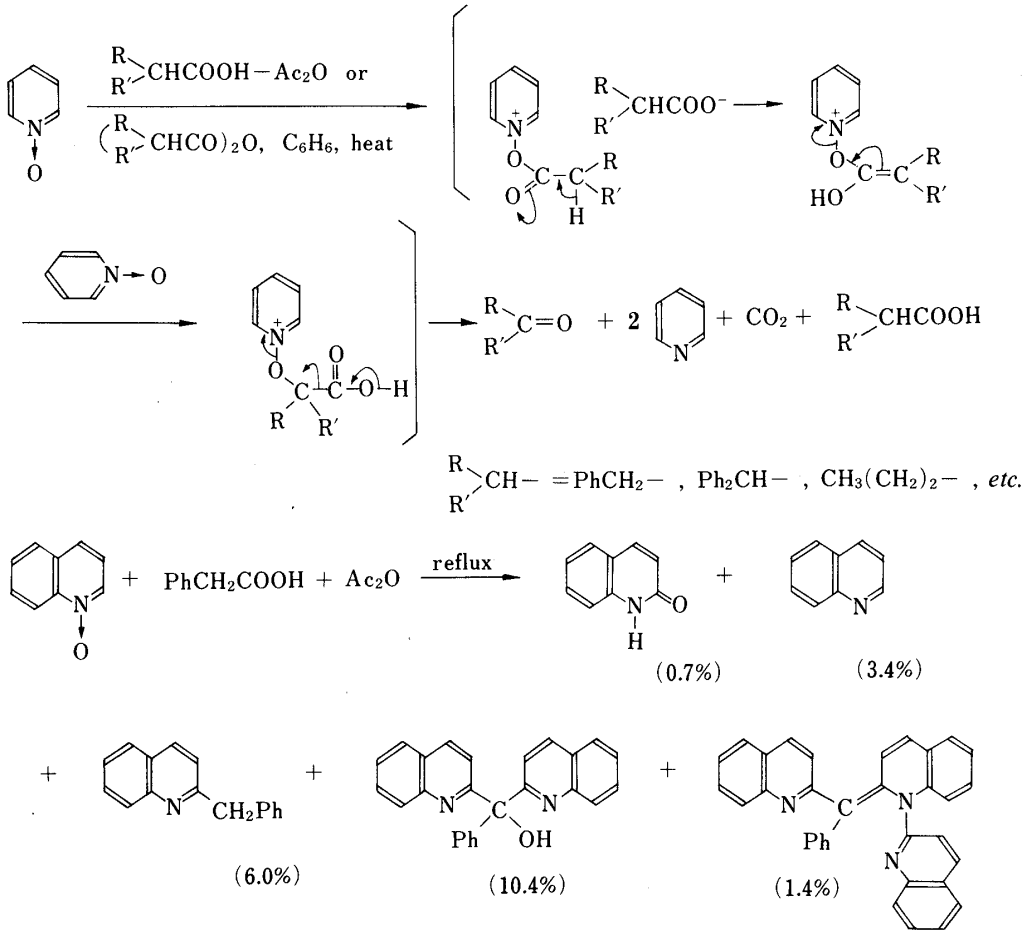

Chart 1

that **8** is obtainable, though in a rather low yield of *ca.* 22%, from the reaction of 2-benzylquinoline (**4**) with 2-chloroquinoline and sodium hydride in refluxing dioxane. These observations as well as the close similarity of its physical and chemical behavior to those of *N*-(2-quinolyl)-2-(2-quinolylmethylene)-1,2-dihydroquinoline[7] indicate that **8** is not phenyldi(2-quinolyl)methane but *N*-(2-quinolyl)-2-benzylidene-1,2-dihydroquinoline.

The reaction of **1** with phenylacetic anhydride in boiling benzene gave a somewhat different result. Thus, a solution of **1** and an equimolar amount of phenylacetic anhydride in benzene was refluxed for 10 h to give 1,3-diphenyl-1-(2-quinolyl)acetone (**9**; 2.4%) and dibenzyl ketone (**10**; 42.4%) together with small amounts of **2** (3.2%), **3** (22.1%), and **5** (1.1%) (reaction (II) in Chart 2).

Compound **9** had the empirical formula $C_{24}H_{19}NO$ and was oxidized with 30% hydrogen peroxide in hot acetic acid to quinaldic acid 1-oxide and phenylacetic acid in 50.0 and 53.6% yields, respectively. Its structure was established by direct comparison with an authentic sample prepared by treatment of **1** with **10** in the presence of acetic anhydride. The IR spectrum of **9** exhibited a strong absorption at 1633 cm^{-1} indicative of a chelated carbonyl group and the NMR spectrum showed a one-proton broad singlet at δ 16.70 due to an NH resonance and a one-proton doublet at δ 6.45 (J=8.9 Hz) assigned to C_3–H of the quinoline ring. From these observations as well as by analogy with the cases of quinaldyl ketones,[11] it may be considered that **9** exists mainly in the chelated enamine form (**9c**), the keto (**9a**) and the enolic forms (**9b**) being negligible.

Compound **2** and at least a part of **3** are considered to be produced by oxidative decarboxylation, but this is not the main path in reactions (I) and (II). The formation of **4**, **5**,

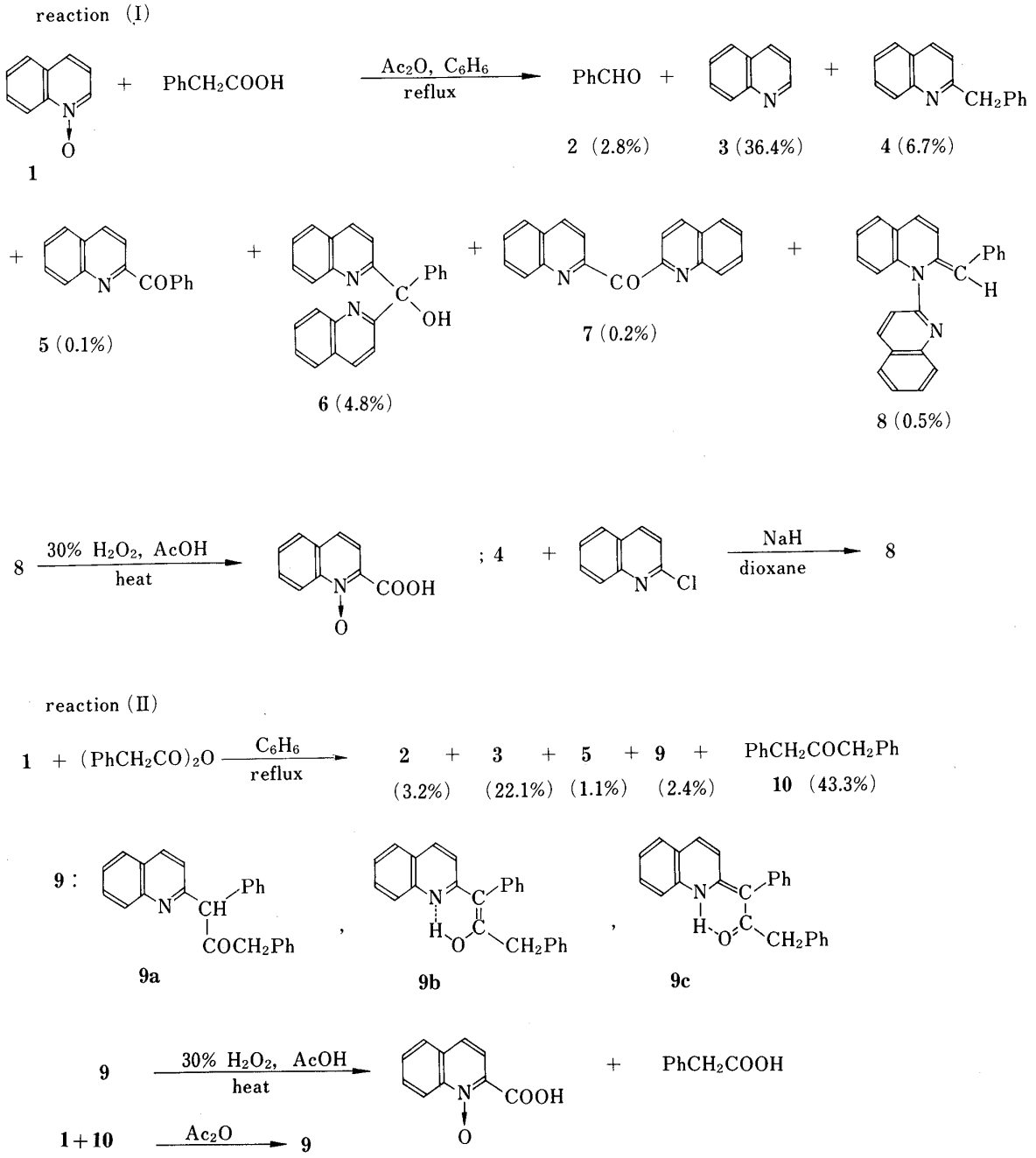

Chart 2

6, and **8** in reaction (I) may be rationalized in terms of the reaction of *N*-acetoxyquinolinium acetate (A) with phenylacetic acid, and we tentatively propose the course illustrated in Chart 3. The phenylacetate anion derived from phenylacetic acid and the acetate anion of A readily undergoes decarboxylation to give the benzyl anion, which attacks at the 2-position of the cation of A followed by elimination of acetic acid to produce **4**. Air oxidation of **4** yields **5**, and nucleophilic reaction of **4** with a second molecule of A gives **8** and di(2-quinolyl)-phenylmethane (B) which is oxidized to **6**. Compound **7** is assumed to be formed by oxidation of di(2-quinolyl)methane formed in the previously described manner from **1** and acetic anhydride.[7]

On the other hand, *N*-phenylacetoxyquinolinium phenylacetate (C) initially formed in reaction (II) undergoes nucleophilic attack by the benzyl anion in two ways. The first is the

same as in reaction (I) giving **5** through **4**. The second is nucleophilic attack at the carbonyl function of the *N*-phenylacetoxy group of C followed by cleavage to **10** and **1**. The formation of **9** can be explained by the reaction of C with **10**. Apparently the decarboxylative coupling to give **10** is the dominant path in this case.

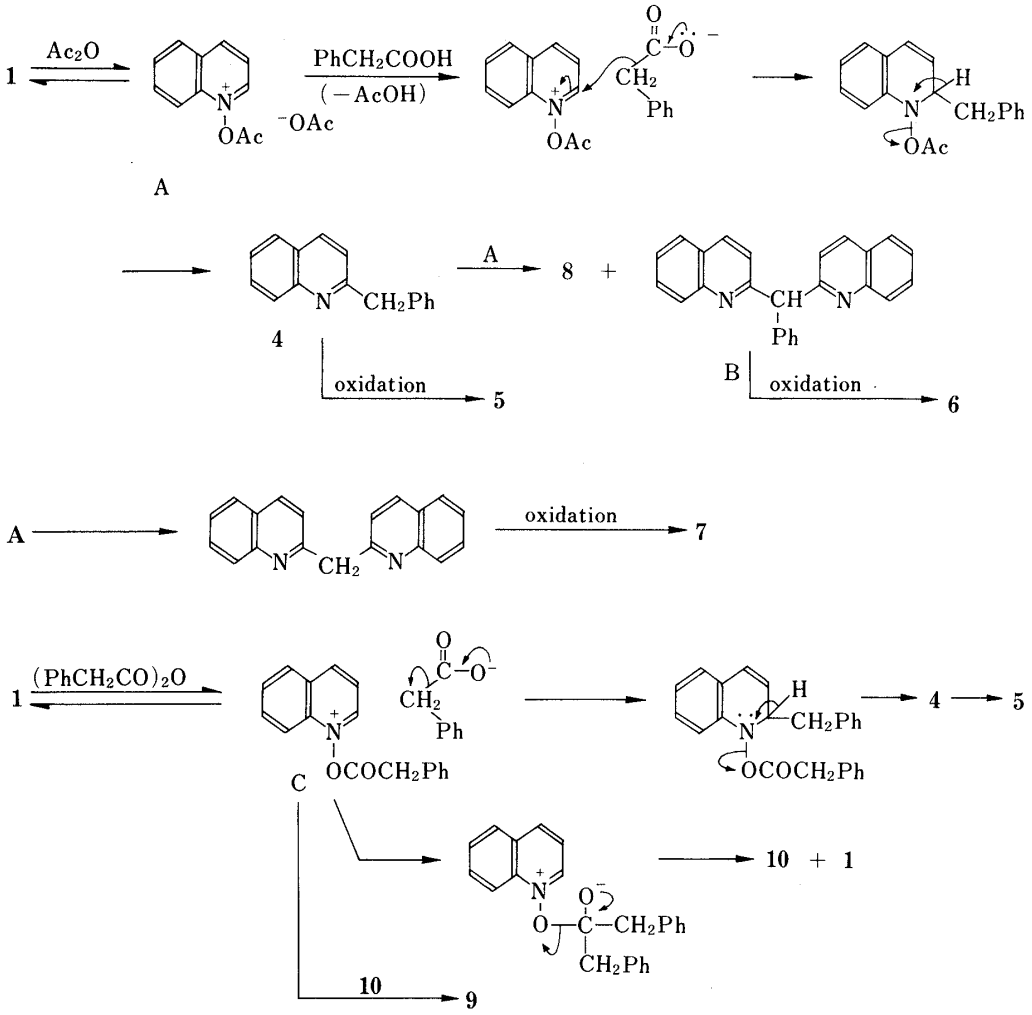

Chart 3

Although the results under various other conditions remain to be explored, the reaction of phenylacetic anhydride with **1** is likely to follow a fairly different path from that with pyridine 1-oxide.

Of particular interest is the formation of **10**, in which **1** acts as a catalyst. In exploring this aspect, reactions of **1** with phenylacetic anhydride were carried out at various molar ratios, and the yields of **3**, **9**, and **10**, and recovery of **1** were determined. In all runs, **10** was obtained in fair to high yields and **1** was recovered in generally satisfactory yields as shown in Table I. Thus it was found that the oxidative decarboxylation of phenylacetic anhydride is only a minor path whereas its decarboxylative coupling to **10** is the major one in the reaction of phenylacetic anhydride with **1**.

These results suggest that tertiary amines may also be able to act as a catalyst for decarboxylative coupling of phenylacetic anhydride. This was confirmed by using several tertiary amines as summarized in Table II.

In order to test the generality of the decarboxylative coupling described above, further experiments with a variety of carboxylic anhydrides are required.

TABLE I. Formation of **3**, **9**, and **10** in the Reaction of **1** with Phenylacetic Anhydride

Mole ratio $\mathbf{1}/(PhCH_2CO)_2O$	Yield (%)			Recovery (%)
	3[a]	**9**[a]	**10**[b]	**1**[a]
1:1	15.8	2.1	43.3	64.4
1:2	16.2	5.9	64.4	40.5
1:6	39.9	2.2	92.2	30.7
1:0.25	5.6	—	84.3	82.7

a) Based on **1**. *b*) Based on phenylacetic anhydride.

TABLE II. Reaction of Phenylacetic Anhydride with Tertiary Amines

Tertiary amine (g)		$(PhCH_2CO)_2O$ (g)	Yield of **10** (%)
Quinoline	7.8	15.26	92.4
Pyridine	1.0	7.26	61.0
Triethylamine	1.0	7.26	79.4
N-Methylpyrrolidine	1.0	7.26	47.0
N-Methylmorpholine	1.0	7.26	46.5
Triethylenediamine	1.0	7.26	27.9
Isoquinoline	1.0	7.26	42.9

Experimental[12]

Reaction of Quinoline 1-Oxide (1) with Phenylacetic Acid and Acetic Anhydride——A solution of **1** (8.70 g), phenylacetic acid (9.80 g) and Ac_2O (6.50 g) in benzene (40 ml) was refluxed for 10 h. The reaction mixture was distilled at *ca.* 110 °C under reduced pressure (50 Torr), and the distillate was concentrated and diluted with EtOH (5 ml). An excess of phenylhydrazine and a small amount of AcOH were added to the EtOH solution, and the mixture was refluxed for 12 min, made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The residue from the extract was chromatographed on alumina with benzene to give 0.34 g (2.8%) of benzaldehyde phenylhydrazone, colorless needles, mp 155—157 °C (hexane).

The mixture of products remaining after distillation was made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The residue from the extract was chromatographed on alumina. Elution with hexane gave successively 2.83 g (36.4%) of quinoline (**3**), bp 73 °C (0.85 Torr), 0.88 g (6.7%) of 2-benzylquinoline[8] (**4**), bp 138—140 °C (0.60 Torr), 0.02 g (0.1%) of 2-benzoylquinoline[9] (**5**), mp 106—107 °C, and 0.54 g (4.8%) of phenyl-di(2-quinolyl)carbinol[7] (**6**), colorless prisms, mp 176—177 °C (acetone). Subsequent elution with benzene gave 0.02 g (0.2%) of di(2-quinolyl) ketone[10] (**7**), colorless needles, mp 163—165 °C (hexane), and 0.05 g (0.5%) of *N*-(2-quinolyl)-2-benzylidene-1,2-dihydroquinoline (**8**), yellow needles, mp 238—240 °C (benzene–hexane). *Anal.* Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.52; H, 5.10; N, 8.05. Compound **8** was identical with an authentic sample prepared from 2-chloroquinoline and **4** as mentioned below.

Oxidation of 8——A solution of **8** (0.20 g) and 30% H_2O_2 (2 ml) in AcOH (5 ml) was heated on a water bath for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from EtOH–H_2O to give 0.04 g (36.4%) of quinaldic acid 1-oxide,[7] colorless needles, mp 164—166 °C (dec.).

Preparation of 8——A solution of **4** (0.88 g) and 50% NaH (0.20 g) in dioxane (10 ml) was refluxed for 2 h, then a dioxane solution of 2-chloroquinoline (0.70 g) was added, and the whole was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The residue from the extract was chromatographed on alumina with hexane and $CHCl_3$. The fraction eluted with hexane–$CHCl_3$ (9:3) was recrystallized from benzene–hexane to give 0.13 g (*ca.* 22%) of **8**, pale yellow needles, mp 238—240 °C.

Reaction of 1 with Phenylacetic Anhydride——1) A solution of **1** (8.70 g) and phenylacetic anhydride (15.24 g, 1 eq) in benzene (40 ml) was refluxed for 10 h. The reaction mixture was processed in the same way as described for the reaction of **1** with phenylacetic acid–Ac_2O to give 0.38 g (3.2%) of benzaldehyde phenylhydrazone, 1.71 g (22.1%) of **3**, 0.16 g (1.1%) of **5**, 5.45 g (43.3%) of dibenzyl ketone (**10**), bp 117—120 °C (0.6 Torr) (oxime: mp 123—

124 °C, phenylhydrazone: mp 125—127 °C), and 0.48 g (2.4%) of 1,3-diphenyl-1-(2-quinolyl)acetone (**9**), golden yellow scales, mp 102—104 °C (EtOH). *Anal.* Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C. 85.36; H, 5.67; N, 4.19. IR ν_{max}^{Nujol} cm^{-1}: 1633 (C=O). NMR ($CDCl_3$) δ: 3.55 (2H, s, $PhC\underline{H}_2CO$), 6.45 (1H, d, J=8, 9 Hz, quinoline C_3–H), 7.12—7.55 (15H, m, Ar–H), 16.70 (1H, br, NH). MS *m/z*: 337 (M^+).

2) A solution of **1** (8.70 g) and phenylacetic anhydride (15.24 g) in benzene (40 ml) was refluxed for 10 h. The reaction mixture was concentrated under reduced pressure, made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The $CHCl_3$ extract was shaken with 10% HCl and the $CHCl_3$ solution and the acidic solution were separated. The residue from the $CHCl_3$ solution was chromatographed on alumina with hexane and benzene. The fraction eluted with hexane gave 5.44 g (43.3%) of **10**, bp 128—133 °C (1.2 Torr), and that with benzene gave 0.42 g (2.1%) of **9**, golden yellow scales, mp 102—104 °C (EtOH). The acidic solution was made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The residue from the extract was distilled under reduced pressure to give 1.22 g (15.8%) of **3**, bp 62—67 °C (1.0 Torr) and 5.60 g (64.4%) of **1**, bp 135—140 °C (1.0 Torr).

Similar reactions of **1** (8.70 g) with phenylacetic anhydride (2, 6 or 0.25 eq) in benzene (40 ml) gave the results listed in Table I.

Oxidation of 9——A solution of **9** (1.0 g) and 30% H_2O_2 (5 ml) in AcOH (20 ml) was heated on a water bath for 3 h. The reaction mixture was concentrated under reduced pressure, made alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$ to give no definite product. The mother liquor was acidified with AcOH to pH 4.6 and extracted successively with ether and $CHCl_3$. The ether extract gave 0.20 g (50%) of phenylacetic acid, colorless plates, mp 76 °C (petr. ether), and the $CHCl_3$ extract gave 0.30 g (53.6%) of quinaldic acid 1-oxide.

Preparation of 9——Dibenzyl ketone **10** (2.50 g) was added with stirring to an ice-cooled solution of **1** (1.45 g) and Ac_2O (2.50 g) in *N*, *N*-dimethylformamide (DMF) (10 ml). The reactants were stirred at 0 °C for 3 h and then kept at room temperature for 3 h. The reaction mixture was poured into AcOEt (80 ml) and washed with two 50 ml portions of 10% Na_2CO_3 then with five 80 ml portions of saturated NaCl solution to remove DMF. The AcOEt layer was dried over Na_2SO_4 and the residue from the AcOEt solution was chromatographed on silica gel. The fraction eluted with AcOEt was recrystallized from EtOH to give 0.89 g (26.4%) of **9**, golden yellow scales, mp 102—104 °C.

Reactions of Phenylacetic Anhydride with Tertiary Amines——General Procedure: A solution of phenylacetic anhydride (7.26 g) and tertiary amine (1.0 g) in benzene (40 ml) was refluxed for 14 h. The reaction mixture was washed with three 10 ml portions of 10% HCl to remove unchanged tertiary amine. Dibenzyl ketone **10** was obtained by fractional distillation of residue under reduced pressure.

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