for the reaction of enolate 1 with benzophenone.[14]

EPR Studies. Reactions of Enolate 1 with Ketones 4 and 5. For the EPR studies, the above-named reactions were performed in quartz EPR tubes equipped with ground glass stopcocks under identical conditions used in the product studies. Immediately after mixing the reagents, the measurements of the EPR signal intensities were made at appropriate time intervals. The plot of ln H vs. time, where H represents the height of the first-derivative EPR signal obtained at high modulation and measured in mm, yielded a straight line in the region where the intensity of the EPR signal was decreasing (see Figures 2 and 4). The concentration of radical species was estimated by a comparison of the peak height of the first-derivative EPR signal generated in the reaction being studied with the peak height of the signal obtained from a standard solution of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide-1-oxyl.

Reaction of Enolate 2 with Benzophenone (4). To a cold (−78 °C) solution of LDA, from 2.5 mmol of MeLi, 2.8 mmol of diisopropylamine, and 5.0 mL of THF, was added dropwise and with stirring during 5 min 0.29 g (2.5 mmol) of 2,2-dimethyl-3-pentanone in 2.0 mL of THF. The resulting solution was stirred from −78 to 0 °C for 1 h and the solvent was then evaporated under vacuum. The resulting white solid was redissolved in 14 mL of THF and 0.31 g (1.7 mmol) of benzophenone (4) in 3.0 mL of THF was added all at once. After allowing the solution to stir for 24 h at 25 °C, a 0.50-mL aliquot was taken from the reaction mixture and worked up as described previously. GLC analyses utilizing columns A (for benzophenone) and B (for 2,2-dimethyl-3-pentanone) indicated that no reaction had occurred. After 1 week, the remainder of the reaction mixture was worked up, and the residual oil was placed under vacuum for 4 h. The NMR spectrum was then obtained (CH_3NO_2 in CCl_4 as the internal standard) and found to be that of Ph_2CO (96%).

Effect of Light, *p*-Dinitrobenzene, and Dicyclohexylphosphine on the Reaction of Enolate 1 with Benzophenone (4). The effect of light and the presence of *p*-DNB and DCPH on the rate of reaction of enolate 1 with benzophenone (4) was determined by carrying out four sets of reactions. One set was carried out under ambient laboratory light, another was carried out in a reaction tube wrapped with aluminum foil, and the others were performed in the presence of either 10 mol % *p*-DNB or DCPH (added to a solution of enolate 1 prior to the addition of Ph_2CO) under laboratory light. Aliquots taken from each reaction at appropriate times were worked up and analyzed as described in a previous section. The results of the study are given in Table I.

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Registry No. 4, 119-61-9; 5, 131-58-8; 7, 844-39-3; 8, 63382-94-5; pinacolone, 75-97-8; 2,2-dimethyl-3-pentanone, 564-04-5.

(14) Castellan, G. W. "Physical Chemistry", 2nd ed.; Addison-Wesley: Reading, MA, 1971; pp 737-739.

Polar Effects in Free-Radical Reactions. Selectivity and Reversibility in the Homolytic Benzylation of Protonated Heteroaromatic Bases

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The homolytic benzylation of protonated 4-cyanopyridine, quinoline, 2-methyl- and 4-methylquinoline, isoquinoline, and quinoxaline is investigated. The great influence of the polar effect and of the reversibility of the addition of the benzyl radical on the reaction selectivity is discussed. It is put forward the hypothesis that the HSAB principle can be extended to free-radical reactions when the polar effect is the dominant factor.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals has very large synthetic involvements, which substantially reproduce the numerous aspects of the aromatic Friedel–Crafts alkylation and acylation but with opposite reactivity and selectivity.[1] Since there is a strict relationship between stability of carbonium ions and nucleophilic character of carbon-centered radicals, generally all the Friedel–Crafts reagents useful in aromatic substitution can be utilized, as corresponding radicals, for the selective substitution of protonated heteroaromatic bases.

Recently a quite similar behavior has been observed with different aromatic substrates bearing a positive charge in the aromatic nucleus, the pyrilium salts,[2] further supporting our interpretation that the polar effect is the dominant factor in determining the reactivity of these free-radical reactions. From the regioselectivity and the kinetic behavior (negative activation energy) we have previously obtained evidence[3] that the reactions with *tert*-alkyl and acyl radicals can be reversible and that therefore the equilibrium and the rate of the rearomatization step can play an important role in determining the selectivity.

(1) Minisci, F. *Synthesis* **1973**, 1; *Top. Curr. Chem.* **1976**, *62*, 1; "Fundamental Research in Homogeneous Catalysis"; Plenum Press: New York, 1984; Vol. 4, p 173. Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27. Vismara, E. *Chim. Ind. (Milan)* **1983**, *65*, 34.

(2) Doddi, A.; Ercolani, G., personal communication, Symposium of Organic Chemistry, Sirmione, Italy, Sept 22–27, 1985.

(3) (a) Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* **1977**, *107*, 491. (b) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960. (c) Citterio, A.; Minisci, F.; Franchi, V. *J. Org. Chem.* **1980**, *45*, 4752. (d) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146.

0022-3263/86/1951-0476$01.50/0

Table I. Benzylation of Heteroaromatic Bases by Decarboxylation of $PhCH_2COOH$ by $S_2O_8^{2-}$

heteroaromatic base	T, °C	bibenzyl (I), mmol	benzyl heteroaromatic (II), mmol	II:I
4-cyanopyridine	40	0.23	1.61	7.0
	60	0.40	1.94	4.8
	80	0.50	1.99	3.9
	100	0.67	1.62	2.4
quinoline	40	0.19	2.04	10.7
	100	0.32	1.71	5.3
2-methylquinoline	40	1.03	1.20	1.2
	100	1.63	0.60	0.36
4-methylquinoline	40	1.40	0.19	0.13
	100	2.15	0.07	0.03
isoquinoline	40	trace	0.47	>30
	100	0.14	0.82	5.8
quinoxaline	100	-	1.16	>100
quinoxaline[a]	100	0.21	1.52	7.2

[a] A buffered solution of $PhCH_2COOH$ and $PhCH_2COONa$ was used.

Table II. Benzylation of Heteroaromatic Bases by Oxidation of Toluene

heteroaromatic base	T, oxidant °C	bibenzyl (I), mmol	benzyl heteroaromatic (II), mmol	II:I
4-cyanopyridine	110 perkadox 16[a]	0.92	0.23	0.25
quinoline	60 perkadox 16	0.53	1.51	2.8
	110 perkadox 16	0.56	0.65	1.1
quinoxaline	60 perkadox 16		1.26	>100
	110 perkadox 16		1.62	>100
4-cyanopyridine[b]	80 $S_2O_8^{2-}$	0.13	0.81	6.2

[a] Perkadox 16 = bis(4-*tert*-butylcyclohexyl) percarbonate. [b] Acetonitrile–water (1:1) as solvent.

Now the extent of the reversibility mainly depends on the reaction enthalpy and therefore on the stability of the attacking carbon-centered radical. Thus we can foresee that also the addition of the benzyl radical to the heteroaromatic ring can be a reversible process. Evidence of this reversibility and the involvements on the positional and substrate selectivity and on the general synthetic interest of the homolytic benzylation are reported in this paper.

Results and Discussion

4-Cyanopyridine, quinoline, 2-methylquinoline, 4-methylquinoline, isoquinoline, and quinoxaline were investigated as heteroaromatic bases. Different sources of benzyl radicals were utilized:[1] oxidative decarboxylation of phenylacetic acid, mediated or not by silver salt and oxidation of toluene by dialkyl percarbonate or ammonium peroxydisulfate.

The conversions of the base were not kept high in order to minimize the formation of disubstituted derivatives when two nuclear positions are activated, as in 4-cyanopyridine, quinoline, and quinoxaline.

With quinoxaline all the benzyl radicals produced are trapped by the base and 2-benzylquinoxaline is substantially the only reaction product, unless quinoxaline is only partially protonated.

With all the other bases, in addition to the nuclear benzylation, variable amounts of bibenzyl are formed. The ratio between bibenzyl and the benzyl derivative of the heteroaromatic base is affected by the temperature in all cases, and the results are summarized in the Tables I and II.

As concerns the positional selectivity only the α- and γ-positions are attacked so that 4-cyanopyridine, 2-methyl- and 4-methylquinoline, and quinoxaline give a single isomer; also isoquinoline is, however, attacked only in the position 1. Quinoline gives rise to two isomers (2- and 4-benzyl) and the isomer ratio is greatly affected by the reaction conditions; the results are reported in Table III.

Four different mechanisms of generation of the benzyl radical are involved:[1] (i and ii) oxidative decarboxylation of phenylacetic acid by peroxydisulfate, mediated (eq 1 and 2) or not (eq 3) by silver salt; (iii) hydrogen abstraction

$$S_2O_8^{2-} + 2Ag^+ \rightarrow 2SO_4^{2-} + 2Ag^{2+} \quad (1)$$

$$PhCH_2COOH + Ag^{2+} \rightarrow PhCH_2\cdot + CO_2 + H^+ + Ag^+ \quad (2)$$

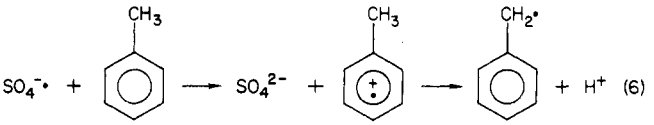
$$PhCH_2COO^- + SO_4^{-}\cdot \rightarrow PhCH_2\cdot + CO_2 + SO_4^{2-} \quad (3)$$

from toluene by alkoxy radicals generated from dialkyl percarbonate (eq 4); (iv) electron-transfer oxidation of

$$PhCH_3 + RO\cdot \rightarrow PhCH_2\cdot + ROH \quad (4)$$

toluene by peroxydisulfate (eq 5 and 6).

$$S_2O_8^{2-} \rightarrow 2SO_4^{-}\cdot \quad (5)$$

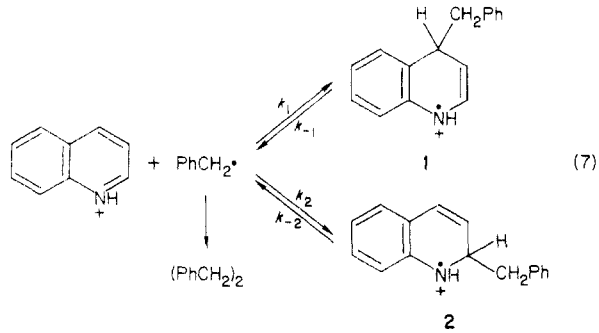


The fate of the benzyl radical is shown by the reaction products: (a) dimerization to bibenzyl when a suitable stationary concentration of the benzyl radical is achieved; (b) addition to the heterocyclic ring to give substitution products. No significant oxidation of the benzyl radical to benzyl alcohol, benzaldehyde, or benzoic acid was observed, if oxygen was carefully excluded. The overall reaction mechanism must account essentially for the ratios between bibenzyl and products of heteroaromatic benzylation, for the temperature influence and for the positional selectivity with quinoline.

In all cases the ratio between bibenzyl and products of heteroaromatic benzylation increases by increasing the temperature. We explain this fact by the reversibility of the addition of the benzyl radical to the heteroaromatic ring (eq 7). Increasing the temperature increases the stationary concentration of the benzyl radical, which irreversibly dimerizes. The absolute rate constants for the addition of the alkyl radicals to the protonated bases are

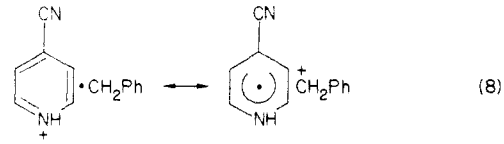
Table III. Isomer Distribution in the Benzylation of Quinoline

T, °C	solv	radical source	oxidant	2-benzylquinoline, %	4-benzylquinoline, %
40	water	$PhCH_2COOH$	$S_2O_8^{2-}$	13	87
100	water	$PhCH_2COOH$	$S_2O_8^{2-}$	13	87
60	toluene	toluene	perkadox 16	51	49
110	toluene	toluene	perkadox 16	55	45
80	acetonitrile–water (1:1)	toluene	perkadox 16	18	82
100	water		$S_2O_8^{2-}$	14	86



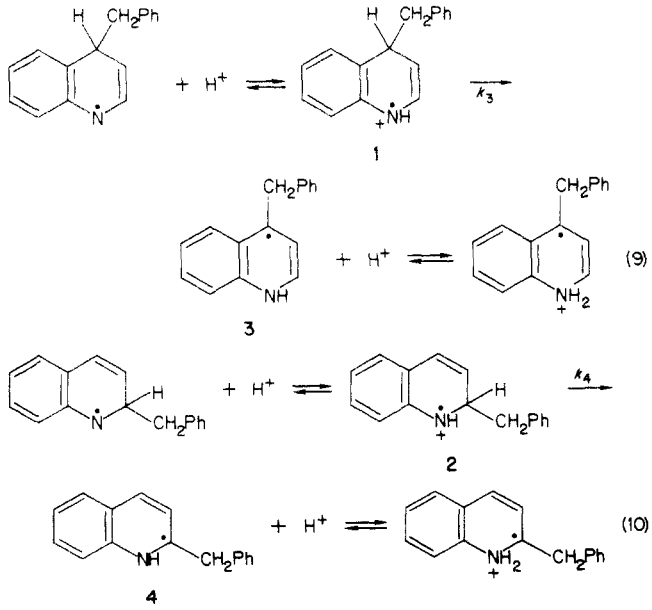
rather high[3] (10^5–10^7 M^{-1} s^{-1}); *tert*-alkyl[3c] and hydroxymethyl[4] radicals are more reactive than primary alkyl radicals, indicating that the polar effect is more important than the enthalpic effect in determining the reactivity. Thus also for the benzyl radical a relatively high addition rate can be foreseen, and it would be inconsistent with a stationary concentration of the benzyl radical suitable for the dimerization, unless the process is reversible.

The exclusive formation of the α- and γ-benzyl derivatives further indicates that the polar effect is the dominant factor in determining reactivity and selectivity, and a transition state similar to charge-transfer complex (eq 8) can be envisaged. No benzylation occurs in the absence



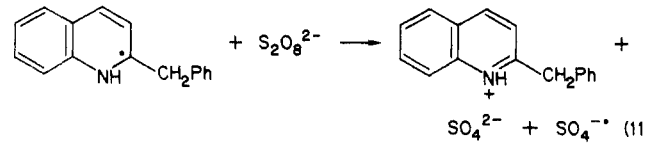
of the protonation of quinoline, and only bibenzyl is formed.

The further evolution of the radical adducts **1** and **2**, according to our recent interpretation,[3d] is determined by the irreversible loss of an α- or γ-position, giving the pyridinyl-type radicals **3** and **4** (eq 9 and 10). **3** and **4** are



weakly basic and strongly nucleophilic radicals and they are selectively oxidized by the radical source (i.e., eq 11).

The fact that with protonated quinoxaline, no bibenzyl is formed with different radical sources and at different temperatures suggests that in this case the addition of the benzyl radical is substantially irreversible. In our opinion



this behavior cannot be ascribed to a substantial difference in reaction enthalpy between quinoline and quinoxaline but to the kinetic features involving the rates of addition of the benzyl radical and the irreversible loss of proton of the radical adduct. Both these rates must be significantly higher with protonated quinoxaline,[3] which is a more electron-deficient base, and they contribute to make practically irreversible the benzylation process. In a buffered reaction medium, in which quinoxaline is only partially protonated, some bibenzyl is formed (Table II)

An intriguing aspect is the positional selectivity in the benzylation of quinoline, which is strongly influenced by the reaction conditions. The ratio between the isomer **4** and **2** appears to be independent of the radical source but highly dependent on the reaction medium. In toluene the two isomers are formed in comparable amounts; in water the isomer **4** greatly prevails over the isomer **2**, and that is further supported by the higher yields of the benzyl derivative and less bibenzyl obtained with 2-methyl- rather than with 4-methylquinoline under identical reaction conditions.

A possible explanation is that the position 4 of protonated quinoline is more reactive than position 2 ($k_1 > k_2$), but the loss of the proton is faster with **2** than with **1** ($k_4 > k_3$) because of the proximity of the positive charge. The loss of the proton on the other hand is faster in water than in toluene, and therefore we can expect that between k_4 and k_3 the difference is more discriminating in toluene. Thus in toluene the higher rate of addition of the benzyl radical to the position 4 of quinoline is counterbalanced by the higher reversibility of the adduct **3** and comparable amounts of the isomers **2** and **4** are obtained, whereas in water the faster loss of the proton makes less discriminating the reversibility between adducts **3** and **4** and the large prevalence of the isomer **4** more closely reflects the difference between k_1 and k_2. This explanation is supported by the fact that at the same temperature the ratio between bibenzyl and the product of the heteroaromatic benzylation is higher in toluene than in water, indicating a more marked degree of reversibility in toluene as consequence of the slower loss of the proton (eq 9 and 10). In this context the question arises why the position 4 of protonated quinoline is more reactive than position 2 considering that position 2 has a lower electron density than position 4.

For ionic nucleophilic substitutions it is known[5] that 1-alkylquinoline salts undergo 4-substitution with the weak CN^- nucleophile but only 2-substitution when a stronger nucleophile such as OH^- is employed, and similar behavior[6] has been observed with pyridinium ions, and attempted explanations by the perturbation method have been reported.[6,7]

The HSAB (hard and soft acids and bases) principle, however, simply explains, in our opinion, this trend: the position 2 in the quinolinium ion is harder than the position 4 so that a hard nucleophile (OH^-) reacts in position 2 and a soft nucleophile (CN^-) in position 4. Many calculations and NMR analyses[8] indicate that the electron

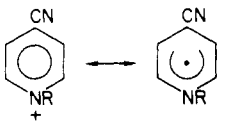
(4) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *Tetrahedron* **1985**, *41*, 617.

(5) Bradley, W.; Jeffrey, S. *J. Chem. Soc.* **1954**, 2770.
(6) Hudson, R. F. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 36.
(7) Chalvet, O.; Dandel, R.; McKillop, T. F. W. *Tetrahedron* **1970**, *26*, 349.

densities of the positions 2 of quinoline, protonated quinoline, and *N*-alkylquinolinium salts are lower than the electron densities of the positions 4.

The extension of the HSAB principle to the nucleophilic radicals, in the sense that the softness of a nucleophilic radical generally increases by decreasing the ionization potentials (similarly the softness of the ionic nucleophiles increases by decreasing the ionization potentials, which are roughly the energies of the HOMO s[9]), leads to the indication that the softer the nucleophilic radical is, the more he position 4 is attacked in comparison with the position 2 of protonated quinoline. The benzyl radicals are softer (lower ionization potential and higher polarizability) than the alkyl radicals, and that determines an increased attack of the position 4 of protonated quinoline.

The phenomenon would seem to be general with carbon-centered radicals; among the alkyl radicals the softness increases according to sequence CH_3 < primary alkyl < secondary alkyl < tertiary alkyl, and the same sequence has been qualitatively observed[1] in the ratio of isomer **4**–isomer **2** with protonated quinoline and pyridine with the exception of *tert*-alkyl radicals which do not attack the position 4 of quinoline for steric reasons (this exception does not exist with pyridine). The similarity of behavior between nucleophilic free radicals and ionic nucleophilic species would suggest something common in the transition states of the two reactions. That could be envisaged in a charge-transfer character of the transitions states in both reactions (eq 8 for nucleophilic free radical and eq 12 for ionic nucleophiles) and it would agree with the model



(12)

developped by Shaik and Pross[10] for ionic nucleophilic substitutions, in which an electron-transfer configuration of the type of eq 12 could contribute to a greater or lesser extent depending on the donor properties of the nucleophile and the acceptor properties of the substrate.

In conclusion, the reversibility appears to be an important aspect of the benzylation of protonated heteroaromatic bases. From a synthetic point of view the reaction becomes even more interesting by increasing the electron deficiency of the heteroaromatic base and decreasing the reaction temperature. Moreover, the regioselectivity must be considered in any case very carefully and the relative rates determined by competitive kinetics[11] may be invalidated by the present results.

(8) Jones, G., Ed. "The Chemistry of Heterocyclic Compounds—Quinolines"; Wiley: London, 1977; Part J, p 1.
(9) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: London, 1976, p 37.
(10) Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3692. Pross, A.; Shaik, S. S. *Ibid.* **1981**, *103*, 3702; *Tetrahedron Lett.* **1982**, *23*, 5467.
(11) Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* **1973**, *28*, 2775.

Experimental Section

Benzylation by Phenylacetic Acid. (A) Silver Catalyzed Oxidation by $S_2O_8^{2-}$. A mixture of heteroaromatic base (3.8 mmol), $PhCH_2COOH$ (12 mmol), H_2SO_4 (3.8 mmol), $(NH_4)_2S_2O_8$ (3.8 mmol), and $AgNO_3$ (0.7 mmol) in 20 mL of water was warmed for 3 h in a nitrogen atmosphere at the temperatures reported in the Table I. The solution was made basic by 5% NaOH and extracted with ether. The solution was analyzed by GLC (quinaldine or lepidine as internal standard by using Carlo Erba 4200 instrument, SP4100 integrator glass column packed with OV 17 3% GCPS 100/120). The results are reported in Table I.

Bibenzyl and benzyl derivatives of the bases were identified by isolation by silica gel chromatography and comparison with authentic samples[1] (IR, NMR, MS).

(B) Thermal Oxidation by $S_2O_8^{2-}$. A mixture of quinoxaline (3.9 mmol), $PhCH_2COOH$ (8 mmol), $PhCH_2COONa$ (8 mmol), and $(NH_4)_2S_2O_8$ (4 mmol) in 20 mL of water was warmed for 2 h at 100 °C in a nitrogen atmosphere. The solution was made basic by 5% NaOH, extracted with ether, and analyzed by GLC. The results are reported in Table I.

Benzylation by Toluene. (A) By Perkadox 16 in Toluene Solution. The solution of the heteroaromatic base (3.8 mmol), CF_3COOH (8 mmol), perkadox 16 (bis(4-*tert*-butylcyclohexyl) percarbonate) (3.8 mmol) in 18 mL of toluene was warmed for 4 h in nitrogen atmosphere at the temperature reported in Table II. The solution was washed with 5% NaOH and analyzed by GLC (quinaldine as internal standard). The results are reported in Table II.

(B) By Perkadox 16 in a MeCN–H_2O Mixture. A mixture of toluene (5 mL), quinoline (3.8 mmol), H_2O (10 mL), MeCN (10 mL), Perkadox 16 (3.8 mmol), and CF_3COOH (8 mmol) was warmed at 80 °C for 4 h. Two phases are present during the reaction. The mixture was made basic by 5% NaOH, extracted with ether, and analyzed by GLC. The conversion of quinoline is very low (3%), due to the heterogeneous reaction medium. The isomer distribution is reported in Table III.

(C) By $(NH_4)_2S_2O_8$ in a MeCN–H_2O Mixture. A mixture of 4-cyanopyridine (3.8 mmol), toluene (20 mmol), H_2SO_4 (4 mmol), $(NH_4)_2S_2O_8$ (4 mmol), $AgNO_3$ (0.7 mmol), MeCN (10 mL), and H_2O (10 mL) was warmed for 3 h in nitrogen atmosphere at 80 °C. The solution was made basic by 5% NaOH, extracted with ether, and analyzed by GLC. The results are reported in Table II.

(D) By $(NH_4)_2S_2O_8$ in Water. A mixture of quinoline (3.8 mmol), H_2SO_4 (4 mmol), $(NH_4)_2S_2O_8$ (4 mmol), toluene (5 mL), and water (20 mL) was warmed at 100 °C for 4 h. The mixture was made basic by 5% NaOH, extracted with ether, and analyzed by GLC. Also in this case, due to the heterogeneous medium, the conversion of quinoline is very low (4%). The isomer distribution is reported in Table III.

Acknowledgment. This work was supported by Progetto Finalizzato Chimica Fine e Secondaria, CNR.

Registry No. $PhCH_2CO_2H$, 103-82-2; $PhCH_3$, 108-88-3; $Ph(CH_2)_2Ph$, 103-29-7; 4-cyanopyridine, 100-48-1; 2-benzyl-4-cyanopyridine, 18251-51-9; quinoline, 91-22-5; 2-benzylquinoline, 1745-77-3; 4-benzylquinoline, 5632-14-4; 2-methylquinoline, 91-63-4; 4-benzyl-2-methylquinoline, 99749-18-5; 4-methylquinoline, 491-35-0; 2-benzyl-4-methylquinoline, 99749-19-6; isoquinoline, 119-65-3; 1-benzylisoquinoline, 6907-59-1; quinoxaline, 91-19-0; 2-benzylquinoxaline, 31102-97-3.