RECYCLIZATION OF 2-BENZYLPYRIDINIUM SALTS TO 2-AMINOBIPHENYLS

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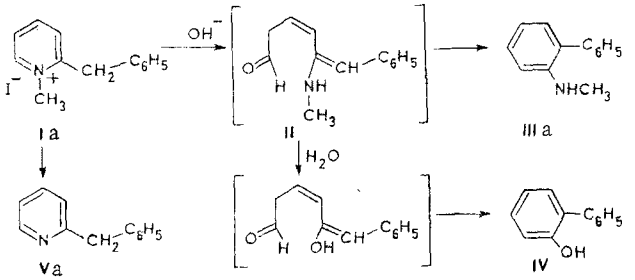
Under the influence of aqueous solutions of alkylammonium sulfites, substituted 2-benzylpyridinium salts undergo rearrangement to 2-aminobiphenyls. The competitive processes that occur during rearrangement of the 2-benzylpyridinium salts were studied.

We have previously shown that quaternary 2-methylpyridinium salts undergo rearrangement with opening of the pyridine ring to N-alkylanilines under the influence of bases [1-3].

In connection with the fact that the C–H acidity of the methylene group in the benzyl grouping is considerably higher than that of the methyl group, one might have expected that replacement of the CH_3 group in the 2 position of the pyridine ring by a benzyl group would promote rearrangement to give 2-aminobiphenyls. Experiments showed that 2-benzylpyridine methiodide (Ia) upon prolonged heating with aqueous alkali solution is actually converted to 2-methylaminobiphenyl (IIIa), although, to be sure, the latter is obtained in only 6% yield in view of the competitive hydrolysis of open intermediate II. However, if the reaction is carried out in an aqueous solution of methylamine, the yield of the corresponding 2-methylaminobiphenyl is increased to 10%. In addition, 2-hydroxybiphenyl (IV) is formed in 9% yield, together with an N-dealkylation product, i.e., 2-benzylpyridine (Va), in 52% yield.



As demonstrated in [2], 2-methylpyridine methiodide does not undergo rearrangement at all under the same conditions.

In comparing our results with the known data on the recyclization of α-picoline [2] we assumed that the sulfite ion, by adding to 2-benzylpyridinium salts, would make it possible to carry out the recyclization to give 2-aminobiphenyls in higher yields. In fact, we obtained 2-alkylaminobiphenyls IIIa-d in 50-80% yields by heating 2-benzylpyridine alkiodides Ia-d with an alkylammonium sulfite [4].

These results make it possible to propose a mechanism that is similar to that described in [2], according to which the sulfite ion, being a soft nucleophile, preferably adds to the softest position in the pyridine ring, i.e., to the $C_{(4)}$ position. The primary product is a 1,4-dihydropyridine of the VI type, which then undergoes ring opening and reclosing with splitting out of the reagent to give an aromatic amine. N-Dealkylation to give 2-benzylpyridines Va, c, d in ∿10% yields takes place simultaneously. The yields of 2-methylaminobiphenyl in the case of recyclization under the influence of alkali and an aqueous alcohol solution of methylamine are lower than in the case of the action of methylammonium sulfite

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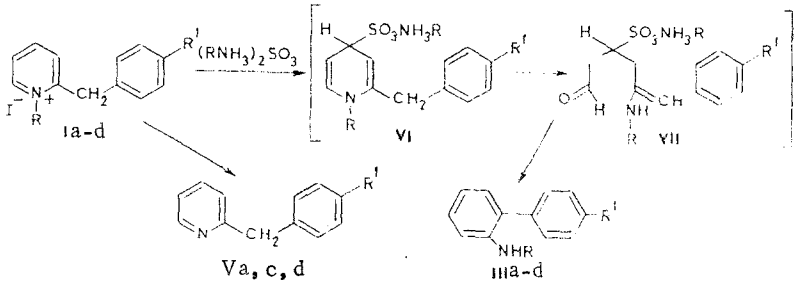
TABLE 1. Recyclization of Pyridine Derivatives

Starting substance	Nucleophile	Final products	mp,[a] °C		Yield, %		
			III	V	III	IV[b]	V
Ia	30% NaOH	— IIIa	96 (A)[c] [7]	Oil	6	—	—
Ia	Alcoholic CH_3NH_2	Va, IIIa	96 (A)	Oil	8	5	46
Ia	Aqueous CH_3NH_2	Va, IIIa	96 (A)	„ „	5	9	52
Ia	$(CH_3NH_3)_2SO_3$	Va, IIIa	96 (A)	„ „	74	—	—
Ib	$(CH_3NH_3)_2SO_3$	Va, IIIa	96 (A)	„ „	61	10	12
Ia	$[(CH_3)_2NH_2]_2SO_3$	Va, IIIa	96 (A)	„ „	5	20	54
Ia	$(NH_4)_2SO_3$	Va, IIIa	96 (A)	„ „	4	14	53
Va	$(CH_3NH_3)_2SO_3$	Va, IIIa	96 (A)	„ „	1	1	54
Ia	$(C_2H_5NH_3)_2SO_3$	— IIIa	—	„ „	36	10	—
Ib	$(C_2H_5NH_3)_2SO_3$	— IIIb	91—92 (A)[c]	—	57	—	—
Id	$(CH_3NH_3)_2SO_3$	— IIId	136—137 (B)	—	50	—	—
Ic	$(CH_3NH_3)_2SO_3$	— IIIc	82—83[c]	—	56	—	—
If	$(CH_3NH_3)_2SO_3$	Vf, IIIf	—	60 [5]	45	—	10
Ig	$(CH_3NH_3)_2SO_3$	Vf, IIIf	—	60 [5]	7	—	25
Ih	$(CH_3NH_3)_2SO_3$	Vh, —	—	Oil	—	—	58
Ii	$(CH_3NH_3)_2SO_3$	Vi, IIIi	Oil	Oil	67	—	13
Vi	$(CH_3NH_3)_2SO_3$	Vi, IIIi	Oil	„ „	6	—	81

[a]Solvents: benzene (A) and hexane (B). [b]This compound had mp 55°C [mp 56°C [8]). [c]Acetyl derivative.

(Table 1) because of the more hydrolytic reaction conditions. The rather high yield of 2-hydroxybiphenyl constitutes evidence for this.

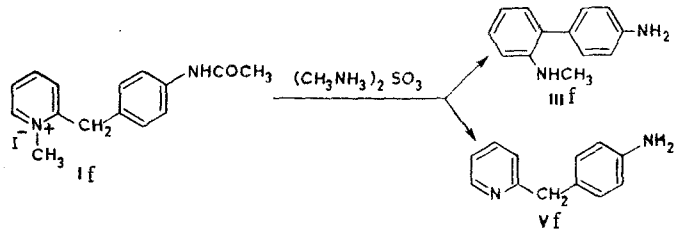


I, III a R=CH_3, R^1=H; b R=C_2H_5, R^1=H; c R=CH_3, R^1=C_2H_5; d R=CH_3, R^1=$COCH_3$; Va R^1=H, c R^1=C_2H_5, d R^1=$COCH_3$

One might have expected that the introduction of an acceptor substituent in the para position of the benzene ring would increase the CH acidity of the methylene group and favor recyclization. However, in the case of heating or at room temperature under the influence of methylammonium sulfite on 2-(p-nitrobenzyl)pyridine methiodide (Ie) the reaction either does not take place at all or (in the second case) leads to the formation of only dealkylation product Ve in 22% yield. Similarly, recyclization does not occur when 2-(p-nitrobenzyl)pyridine methiodide (Ie) is heated with an aqueous alcohol solution of methylamine. The decrease in the nucleophilicity of the β-carbon atom of a noncyclic enamine of the VII type because of the high acceptor character of the p-nitrophenyl group probably does not permit intramolecular condensation of the intermediate and, correspondingly, recyclization here. As compared with 2-(p-nitrobenzyl)pyridine methiodide (Ie), the acetyl group in 2-(p-acetylbenzyl)pyridine methiodide (Id) does not decrease the nucleophilicity of the β-carbon atom of the enamine intermediate to as great a degree as the nitro group, although the yield of 2-aminobiphenyl IIId is lower than in the recyclization of 2-benzylpyridine methiodide.

In order to study the effect of donor substituents from the para position of the benzene ring on the recyclization we studied the quaternization of 2-(p-aminobenzyl)pyridine (Vf) with methyl iodide. However, we found that alkylation does not proceed selectively, and a mixture of salts, in which a compound with an alkylated amino group of the benzene ring is present along with the necessary structure. By using an acetyl protective group we were able to suppress the side reaction involving alkylation of the amino group and obtain an individual compound, viz., 2-(p-acetamidobenzyl)pyridine methiodide (If). Two reaction products were obtained when this methiodide was heated with methylammonium sulfite. The first compound (IVf) was formed in 45-50% yield as a result of rearrangement of the starting

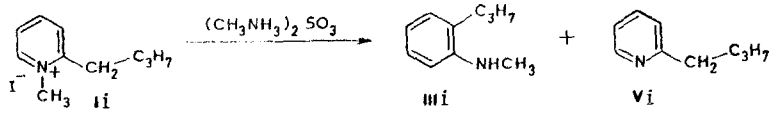
model compound with simultaneous removal of the protective group. The second compound (Vf, 10% yield) is also formed as a result of two processes, viz., N-dealkylation, on the one hand, and removal of the protective acetyl group, on the other.



Similarly, when 2-(p-phthalimidobenzyl)pyridine methiodide (Ig) was heated with methylammonium sulfite, 2-methylamino-4-aminobiphenyl (IIIf) and 2-(p-aminobenzyl)pyridine (Vf) were obtained in 7 and 25% yields, respectively. An increase in the acceptor character of the para substituent in the benzene ring of 2-benzylpyridine evidently also hinders the reaction in this case.

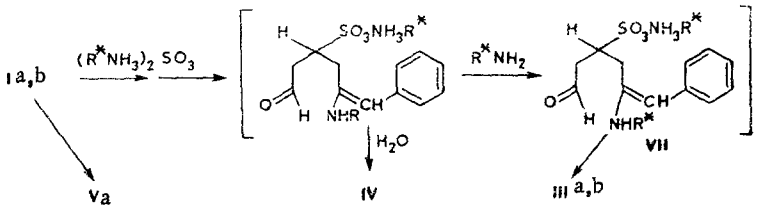
The introduction of alkyl groups in the α and β positions of the pyridine ring of 2-benzylpyridine decreases the electron-deficient character of the ring and creates steric hindrance to the addition of the sulfite ion, which may make recyclization virtually impossible. In fact, the recyclization of 2-benzyl-4,6-dimethylpyridine methiodide (Ih) does not occur at all, and only an N-dealkylation product, viz., 2-benzyl-4,6-dimethylpyridine (Vh), is formed in 57% yield.

If 2-butylpyridine methiodide (Ii) is used as the pyridine salt, N-methyl-2-propylaniline (IIIi) and 2-butylpyridine (Vi) are formed in 67% and 13% yields, respectively, when it is heated with methylammonium sulfite.



Thus, within the framework of our experiments, it may be assumed that the expected activation of the α-methylene group by an aryl substituent is not observed. This is in agreement with the previously expressed assumptions relative to the mechanism of recyclization under the influence of sulfite reagents, in which the formation of anhydro bases from pyridinium salts is not necessary [2].

When a solution of an alkylammonium sulfite with an alkyl group that differs from that in the starting pyridinium salt is used as the recyclizing agent, transamination evidently occurs in the step involving an open intermediate of the VII type. Thus 2-methylaminobiphenyl (61%), 2-hydroxybiphenyl (10%), and 2-benzylpyridine (12%) are formed in the reaction of methylammonium sulfite with 2-benzylpyridine ethiodide (Ib).

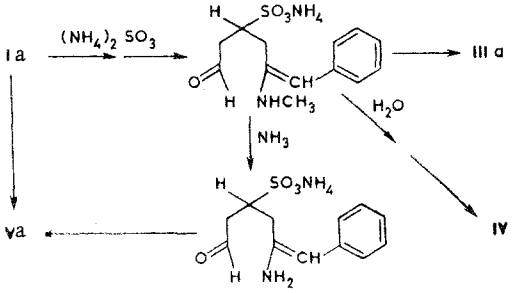


Thus the recyclization of 2-benzylpyridine ethiodide (Ib) proceeds with complete exchange of the N-substituent. In contrast to this, in the reaction of ethylammonium sulfite with 2-benzylpyridine methiodide (Ia) the reaction proceeds primarily to give 2-methylaminobiphenyl (IIIa), i.e., virtually without transamination. 2-Ethylaminobiphenyl (IIIb) is not recorded in the PMR spectrum of the mixture of reaction products, and its formation in trace amounts can be detected only by chromatographic mass spectrometry. The yield of 2-methylaminobiphenyl (IIIa) in this case reaches 36%. In addition, 2-hydroxybiphenyl (IV) is formed in 10% yield.

All of these results indicate that the exchange of the methylamine residue for an ethylamine residue in an open intermediate of the VII type proceeds with difficulty. Secondary amines do not undergo transamination at all. For example, only 2-methylaminobiphenyl

(IIIa, 5-6%), 2-hydroxybiphenyl (IV, 20%), and dealkylation product Va are formed in the reaction of dimethylammonium sulfite with 2-benzylpyridine methiodide (Ia).

From an analysis of the experimental results it may be concluded that exchange of the alkylamino group takes place particularly easily when the steric volume of the attacking nucleophile is minimal, as in the case of the reaction between 2-benzylpyridine ethiodide (Ib) and methylammonium sulfite. If steric hindrance increases during attack by the nucleophile, the yield of the product with inclusion of the reagent decreases and may vanish completely, as, for example, when dimethylammonium sulfite is used as the nucleophile.



We found that an N-unsubstituted 2-aminobiphenyl is not formed in the reaction of ammonium sulfite with 2-benzylpyridine methiodide (Ia). The reaction mixture contains 2-methylaminobiphenyl (IIIa, 2-5%), 2-hydroxybiphenyl (13-15%), and 2-benzylpyridine (Va, 58-60%).

In other words, rearrangement with exchange of the N-substituent does not occur but rather proceeds without exchange, although the product is obtained in low yield. The high yield of 2-benzylpyridine (Va) is evidently explained by its formation by two alternative methods: first, by direct nucleophilic attack by the reagent at the N-methyl group and, second (and this is evidently the principal pathway), by opening of the pyridine ring, exchange of the methylamine fragment for an amine fragment in the open structure, and subsequent ring formation.

We found that the action of aqueous methylammonium sulfite on unquaternized 2-benzylpyridine (Va) leads to opening of the pyridine ring with exchange of the amine fragment for a methylamine fragment and the formation of the product of recyclization of a pyridinium salt, i.e., 2-methylaminobiphenyl (IIIa), although it is obtained in very low yield (1%). However, the bulk of the 2-benzylpyridine was recovered unchanged, and, therefore, if the yield of the recyclization product is based on the converted 2-benzylpyridine (Va), it amounts to 33%.

$$Va \xrightarrow{(CH_3NH_2)_2SO_3} IIIa$$

Similarly, N-methyl-2-propylaniline (IIIi) is formed in 6% yield when 2-butylpyridine (Vi) is heated with methylammonium sulfite for 50 h. These reactions are of interest not only as new examples of exchange recyclization but also as new instances of opening of an unquaternized pyridine ring under the influence of nucleophilic agents.

Thus the recyclization of 2-benzylpyridinium salts to 2-aminobiphenyls makes it possible to obtain 2-aminobiphenyls that can be used for the synthesis of many condensed heterocyclic compounds.

The structures of all of the compounds obtained were proved by a combination of spectral methods (IR, UV,and PMR); mass-spectrometric analysis was performed for two series of compounds, and the principal fragmentation mechanisms were established.

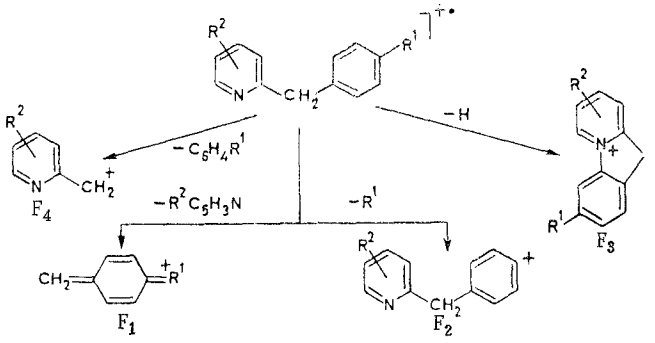
Under the influence of electron impact 2-benzylpyridines Va, c-h form stable molecular ions (Table 2), the fragmentation of which proceeds quite selectively to give four principal fragment ions F_1-F_4 (see the scheme). It should be noted that an increase in the stability of the molecular ion occurs when both electron-acceptor and electron-donor substituents are introduced in the benzene residue; this is probably explained by the absence of conjugation between the benzene and pyridine rings. The positive charge of the molecular ions of these compounds is evidently localized in the pyridine ring. The molecular ion eliminates a hydrogen atom to give benzindolizinium ion F_3. When electron-donor sub-

TABLE 2. Mass Spectra of III and V*

Compound	m/z values (relative intensities, %)
Va	169 (100), 168 (35), 167 (6), 91 (6), 84 (7), 83 (18), 66 (6)
Vc	197 (27), 196 (100), 182 (7), 181 (9), 180 (14), 168 (19), 167 (36), 90 (5), 9 (8), 83 (14), 77 (11)
Vd	211 (60), 210 (100), 208 (17), 196 (23), 169 (8), 168 (54), 167 (68), 166 (16), 139 (7), 90 (7), 89 (9), 83 (14), 63 (8), 50 (12)
Ve	214 (100), 213 (74), 168 (12), 167 (72), 166 (7), 89 (6), 83 (10), 78 (7), 51 (6)
Vf	184 (100), 183 (77), 182 (6), 167 (9), 106 (70), 92 (7), 77 (5)
Vg	314 (100), 169 (7), 168 (20), 167 (8), 130 (9), 104 (3), 77 (5), 76 (30)
Vh	197 (100), 196 (99), 195 (33), 194 (25), 183 (11), 182 (55), 181 (50), 180 (29), 168 (5), 167 (13), 120 (11), 115 (5), 91 (24)
IIIa	183 (100), 182 (62), 181 (15), 180 (39), 168 (23), 167 (57), 166 (20), 165 (36), 154 (7), 153 (12)
IIIb	197 (53), 196 (5), 184 (5), 183 (34), 182 (100), 181 (19), 180 (41), 168 (13), 167 (33), 166 (13), 165 (39), 154 (5), 153 (12)
IIIc	211 (50), 210 (16), 200 (11), 199 (79), 198 (96), 197 (67), 196 (17), 195 (9), 185 (12), 187 (79), 183 (100), 182 (77), 181 (66)
IIId	225 (100), 182 (44), 181 (6), 180 (11), 167 (35), 149 (18), 139 (8), 115 (7)
IIIf	198 (100), 197 (49), 195 (14), 183 (14), 182 (41), 181 (20), 180 (26), 169 (8), 168 (12), 167 (14), 166 (14), 155 (6), 153 (72), 152 (6), 151 (6), 138 (6), 131 (9), 115 (5), 106 (9)

*The molecular-ion peaks and the peaks of ions with intensities up to 5% are presented.

stituents that are capable of p—π conjugation with the benzene ring are present in the molecule, the intensities of the F_1 ion peaks generally increase, whereas in the mass spectra of compounds that contain electron-acceptor substituents the peak of this fragment is either absent or is of very low intensity. On the other hand, the loss of a substituent to give F_2 ions, the peaks of which are rather intense, is characteristic for the molecular ions of these compounds. Finally, in the series of mass spectra one observes peaks of α-picolinium ions F_4, which are characteristic for compounds that contain electron-acceptor substituents. In the remaining cases the F_4 ion peaks are insignificant because of the electron-deficient character of the pyridine ring, which is conjugated with the cationic center.

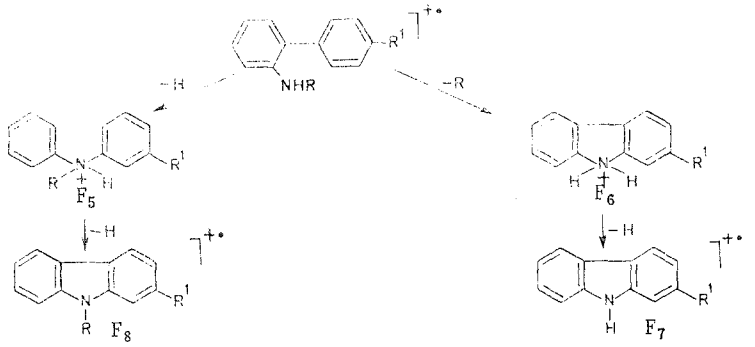


The mass-spectral behavior of the 2-aminobiphenyls obtained (IIIa-d, f) (Table 2) differs markedly from the fragmentation of 2-benzylpyridines and from the pathway of fragmentation of aniline derivatives described in the literature. The stabilities of the molecular ions of 2-methylaminobiphenyls depend to an appreciable degree on the electronic properties of the substituent in the 4 position and on the size and electronic properties of the substituent bonded to the amino group. Donor substituents in the 4 position decrease the stabilities of the molecular ions, whereas acceptor substituents stabilize the molecular ions. The principal pathways of fragmentation of the molecular ions are generally determined by localization of the positive charge on the amino group and are characterized by three principal processes. They involve the loss by the molecular ion of a hydrogen atom, in all likelihood from the other aromatic ring or R; this leads to the formation of relatively stable carbazolium ions F_5 and F_6, which subsequently split out a hydrogen atom to give, respectively, F_8 and F_7 ions. Fragmentation of the substituent located in the second benzene ring generally proceeds only after the formation of the F_8 and F_7 ions.

TABLE 3. Properties of IIIa-i

Compound	R_f[a]	UV spectrum, λ_{max}, nm (log ε)	IR spectrum[b], cm^{-1} (NH)	PMR spectrum, ppm (J, Hz)			
				N—CH_3	NH	aromatic protons	remaining protons
IIIa	0,72 (A)	360 (3,6)	3420	2,8	3,9	6,55—7,6	
IIIb	0,84 (A)	367 (3,6)	3420	—	3,6	6,49—7,59	1,2 (t, CH_3, J=6); 3,01 (q, CH_2, J=6)
IIIc	0,81 (A)	—	3420	2,6	3,8	6,4 —7,3	1,3 (t, CH_3); 2,7 (q, CH_2)
IIId	0,85 (A)	245 (4,3)	3420	2,8	3,2	7,5 —8,5	2,3 (s, $COCH_3$)
IIIf	0,64 (B)	250 (3,98), 310 (2,66)	3420	2,8	3,6 (NH+ NH_2)	6,3 —7,5	—
IIIi	0,61 (A)	—	—	2,67	4,0	6,37—7,00	2,3 (t, CH_3, J=8); 1,23—1,9 (m, 2′-CH_2); 0,83 (t, 3′-CH_3, J=7)

[a]Solvents: benzene (A) and benzene—ethyl acetate (4·1) (B).
[b]In the case of IVd the CO band is found at 1690 cm^{-1}.



EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian T-60 spectrometer with tetramethylsilane and hexamethyldisiloxane as the internal standards. The UV spectra of solutions in ethanol were recorded with a Cary-219 spectrophotometer. The course of the reaction was monitored by means of thin-layer chromatography (TLC) (Silufol UV-254) in benzene and by chromatographic mass spectrometry with a Varian spectrometer at an ionizing-electron energy of 80 eV; the 1.5 m by 3.5 mm column was packed with SE-30 (15%) on Chromopak, and the spectra were recorded with programmed heating from 100 to 250°C at a rate of 10 deg/min. The mass spectra were recorded with an MKh-1303 spectrometer with a modified system for recording with an N105 loop oscillator with introduction of the substances into the ionization region at an ionizing-electron energy of 50 eV, an emission current of 150 mA, and an accelerating voltage of 2 kV.

2-(p-Acetamidobenzyl)pyridine. A 4-ml (38 mmole) sample of acetic anhydride was added to 5 g (27 mmole) of 2-(p-aminobenzyl)pyridine [5], and the mixture was refluxed for 1 h. The acetic anhydride was removed from the reaction mixture by distillation, and the residue was recrystallized from benzene to give 4.63 g (75%) of a product with mp 115-116°C and R_f 0.43 [benzene—ethyl acetate (1:3)]. PMR spectrum (CF_3COOH): 2.49 (s, CH_3), 4.6 (s, CH_2), and 7.2-8.6 ppm (m, aromatic protons). UV spectrum, λ_{max} (log ε): 245 (4.44 and 385 nm (3.59). IR spectrum (mineral oil): 1690 (CO) and 3250 cm^{-1} (NH). Found: C 74.6; H 6.5; N 12.7%. $C_{14}H_{14}N_2O$. Calculated: C 74.3; H 6.2; N 12.4%.

2-(p-Phthalimidobenzyl)pyridine (Vg). A mixture of 5 g (27 mmole) of 2-(p-aminobenzyl)-pyridine [5] and 5 g (5 mmole) of phthalic anhydride was heated at 120°C for 1.5 h, after which the solidified melt was recrystallized from benzene to give 5.8 g (68%) of a product with mp 170°C and R_f 0.56 (benzene). PMR spectrum (CCl_4): 4.2 (s, CH_2) and 7.1-8.0 ppm (m, aromatic protons). UV spectrum, λ_{max} (log ε): 295 (3.36) and 380 nm (1.96). IR spectrum (mineral oil): 1730 cm^{-1} (CO). Found: C 76.4; H 4.5; N 8.8%. $C_{20}H_{14}N_2O_2$. Calculated: C 76.9; H 4.1; N 8.4%.

2-(p-Ethylbenzyl)pyridine (IIIc). A mixture of 5 g (24 mmole) sample of 2-(p-acetylbenzyl)pyridine [6], 5 ml of 85% hydrazine hydrate, 35 ml of ethylene glycol, and 5 g of sodium hydroxide was heated for 6 h, after which it was diluted with water, and the aqueous mixture was extracted with benzene. The extract was evaporated to give 3.23 g (70%) of 2-(p-ethylbenzyl)pyridine with R_f 0.73 [benzene–ethyl acetate (4:1)]. PMR spectrum (CCl_4): 1.2 (t, CH_3, $J_{CH_2CH_3}$ = 8 Hz), 2.55 (q, CH_2, $J_{CH_2CH_3}$ = 8 Hz), and 6.6-7.5 ppm (m, aromatic protons). UV spectrum, λ_{max} (log ε): 260 nm (3.66).

2-Benzylpyridinium Salts (Ia-h). These salts were obtained at room temperature by the reaction of the starting pyridine bases with excess methyl iodide for 12-24 h. The results of elementary analysis for C and H were in agreement with the values calculated for the salts obtained.

Reaction of 2-Benzylpyridinium Salts with Alkyl(dialkyl)ammonium Sulfites. A 20-ml sample of a 25-30% aqueous solution of the alkylamine and 10 ml of a solution of the alkylammonium sulfite, obtained by saturation of an aqueous solution of the alkylamine with gaseous SO_2, were added to 10 mmole of 2-benzylpyridinium iodide dissolved in the minimum amount of water, and the mixture was heated in a sealed ampul at 150°C for 25-30 h. The ampul was opened, and the reaction products were extracted with ether. The ether extract was dried with magnesium sulfate and evaporated, and the residue was separated with a column packed with L100/160 μ silica gel by elution with benzene.

Recyclization of the pyridine bases was carried out as above, except that the mixtures were heated at 180°C for 4-5 days. The final compounds were isolated by the general method.

The properties of the 2-alkylaminobiphenyls are presented in Table 3.

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