Methoxylation–Acetoxymercuration Rates.—The rates of methoxylation–acetoxymercuration of *cis*- and *trans*-1,3-diphenylpropene and of 1,3-diphenylpropyne were determined at room temperature by the procedure of Wright and co-workers.[31] Typically, about 1 mmole of the hydrocarbon was dissolved in absolute methanol (x ml), and the solution was treated with x ml (1 equiv) of a 0.20 M solution of mercuric acetate in absolute methanol. Aliquots of 1 ml were removed at successive time intervals and quenched in water (20 ml) containing 1 ml of saturated potassium nitrate solution, 0.05 M in nitric acid. The mixture from each aliquot was extracted five times with 3-ml portions of chloroform (discarded), and the aqueous layer was rinsed (5 ml of water) into a 125-ml flask and treated with 1 ml of indicator solution (saturated ferric ammonium sulfate in 0.5 M nitric acid). Unchanged mercuric acetate was determined by titration with 0.05 M potassium thiocyanate solution. The resulting rate data are plotted in Figure 1.

Catalytic Hydrogenation of *cis*- and *trans*-1,3-Diphenylpropene.—A sample of *trans*-1,3-diphenylpropene (5.15 mmoles) in ethanol (25 ml) was catalytically reduced at atmospheric pressure in the presence of 30% palladium–charcoal (0.1 g) whereupon 5.29 mmoles of hydrogen was consumed. Similar reductions, involving the expected hydrogen uptake, were conducted with *cis*-1,3-diphenylpropene and 1,3-diphenylpropyne. The 1,3-diphenylpropane products from each reduction had identical infrared and ultraviolet spectra, showed identical retention times on gc, and had $n^{29}\text{D}$ 1.5558. Bromination of *trans*-1,3-diphenylpropene in chloroform solution led to the dibromide described by Dieckmann and Kämmerer,[3] mp 107–109.5°.

Ethylation of 1,3-Diphenyl-2-propanone.—In attempt to prepare the hydrocarbon product, mp 57°, obtained by Francis,[2] the following duplication of his experiment was attempted. Freshly crystallized 1,3-diphenyl-2-propanone (10.00 g, mp 34–34.5°) was dissolved in absolute ethanol (40 ml) and treated with sodium (1.20 g, 1.1 molar equiv) in absolute ethanol (20 ml). The yellow solution was treated with freshly distilled ethyl iodide (8.90 g, 1.2 molar equiv) in absolute ethanol (10 ml) and the mixture was heated under reflux for 2.25 hr, then allowed to stand 18 hr, and poured into water. The mixture was extracted with ether, acidified, and reextracted three times with ether. The combined extracts were washed with 10% aqueous sodium hydroxide, dried, and stripped of solvent, yielding 10.73 g (94.7%) of crude 1,3-diphenyl-2-pentanone as a thin, yellow oil. Tlc (silica, benzene) revealed that the crude product contained some unchanged starting material. The product was characterized as its oxime, which was recrystallized twice from ethanol, mp 89.5°.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.44; H, 7.51; N, 5.53.

The nmr spectrum (60 Mc) accorded with the indicated structure: hydroxyl proton, δ 9.13; aromatic protons, δ 7.23; C-1 benzylic protons, pair of doublets centered, respectively, at δ 4.12 and 3.06 with a coupling constant of 14.5 cps; C-3 proton, pair of doublets centered at δ 3.28 with coupling constants of 7 and 9 cps; C-4 methylene protons, multiplet centered at δ 1.85; C-5 methyl protons, multiplet centered at δ 0.73, coupling constant 7.5 cps. This oxime has been previously reported as having mp 106[2] and 96–97°.[38] It is possible that either polymorphism or geometrical configuration may be responsible for the melting point discrepancies noted.

The bulk of the crude material was distilled at atmospheric pressure. About half showed bp 315–319°, and the remainder foamed too badly to continue. Neither the distillate nor residue deposited crystals on standing for 9 months.

Acidification of the above 10% aqueous alkali wash, followed by extraction with ether, gave a trivial quantity (0.05 g) of acidic material, an amber oil.

Action of Sodium Ethoxide on 1,3-Diphenyl-2-propanone.—A second attempt to obtain Francis' 57° hydrocarbon was made as follows. A mixture of 1,3-diphenyl-2-propanone (10.0 g) and sodium (1.10 g) dissolved in absolute ethanol (70 ml) was heated under reflux for 24 hr, poured into water, and processed as above. The neutral product (10.3 g) was a thick amber oil. About half of it distilled with decomposition at 330–333°. Neither the distillate nor residue crystallized on standing during 9 months. The acidic product (0.2 g) crystallized on standing, and was recrystallized from benzene. It was found by analysis, melting point (168–168.5°), and nmr spectrum to be α-hydroxy-α,β-diphenylpropionic acid.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.45; H, 5.93.

The nmr spectrum (60 Mc) showed 12 protons in the δ 7–7.8 region, indicating that the OH and COOH protons were buried under the ten phenyl protons. The benzylic protons were nonequivalent, as indicated by their appearance as a pair of doublets centered, respectively, at δ 3.22 and 3.60, with a coupling constant of 13.5 cps.

This compound has been reported to have mp 165–166° and to be preparable by passing air through an alkaline solution of 1,3-diphenyl-2-propanone at 70°.[39,40]

Acknowledgment.—W. A. B. gratefully acknowledges the support of a portion of this research by the National Institutes of Health (GM-06232-05).

---

(38) J. Levy and P. Jullien, *Bull. Soc. Chim. France*, **45**, 947 (1929).

(39) O. Widman, *Ber.*, **49**, 484 (1916).

(40) V. Bogdanowska, *ibid.*, **25**, 1276 (1892).

Cyclopropylpyridines. Synthesis and Electronic Interaction[1]

ALLAN P. GRAY AND HAROLD KRAUS

Neisler Laboratories, Inc., Subsidiary of Union Carbide Corporation, Decatur, Illinois

Received June 10, 1965

Carbalkoxy- and cyano-substituted cyclopropylpyridines have been synthesized in two ways: (a) by treatment of the appropriate vinylpyridine with ethyl diazoacetate, and (b) by treatment of 4-picolyl chloride with an acrylate ester or acrylonitrile and sodium hydride in the cold. Gas chromatographic and n.m.r. spectral examination of the products shows that both processes lead to a mixture of the *cis* and *trans* isomers with the *trans* predominating, but that the latter reaction is somewhat more stereoselectively *trans*. The products have been converted to α,α-disubstituted pyridylcyclopropanemethanols by Grignard reactions. The unsubstituted parent system, 4-cyclopropylpyridine, has been obtained in good yield by treatment of 4-pyridylpropyltrimethylammonium chloride with sodamide. Inspection of the ultraviolet and infrared spectra and of the dissociation constants of various of the cyclopropylpyridine derivatives provides evidence of electronic interaction between the cyclopropane and pyridine ring systems. *trans*-2-(4-Pyridyl)-α,α-diphenylcyclopropanemethanol, but not the *cis* isomer, has been found to have interesting psychopharmacological properties.

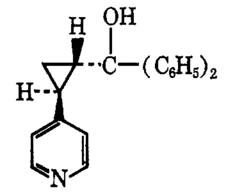
In continuing study of the chemical properties and pharmacological actions on the central nervous system of substituted, particularly 4-substituted, pyridine derivatives,[2] we became interested in ascertaining the effect of attaching a cyclopropane ring directly to the pyridine nucleus. Compounds having such an arrangement could be expected to display properties

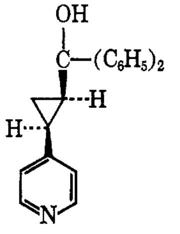
---

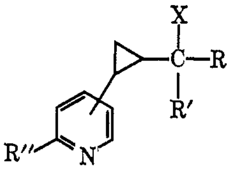
[1] Presented in part before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965.

[2] A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957); A. P. Gray, H. Kraus, and D. E. Heitmeier, *J. Org. Chem.*, **25**, 1939 (1960).

subtly modified by electronic interaction between the two ring systems. Rather intriguingly, an early derivative, *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (I),[3a] but not the *cis* isomer III, was found[3b] to "normalize" the behavior of "neurotic" dogs[4] at doses which had no significant effect on normal animals. Moreover, although I exhibited essentially no monoamine oxidase inhibitory activity,[3] it appeared to be most effective as an antidepressant. These observations prompted extension of the series. The present report deals with the synthesis and chemical properties of a group of these compounds.

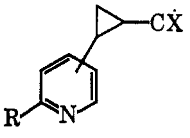

I


III



IV, *trans*-4 isomer; R, R′ = n-C_3H_7; X = OH; R″ = H
V, *cis*-4 isomer; R, R′ = n-C_3H_7; X = OH; R″ = H
VI, *trans*-4 isomer; R, R′ = o-C_7H_7; X = OH; R″ = H
VII, *trans*-4 isomer; R, R′ = C_6H_{11}; X = OH; R″ = H
VIII, *trans*-2 isomer; R, R′ = C_6H_5; X = OH; R″ = H
IX, *trans*-5 isomer; R, R′ = C_6H_5; X = OH; R″ = CH_3
X, *trans*-4 isomer; R = C_6H_5; R′ + X = =O; R″ = H

2-Carbethoxycyclopropylpyridines (II, IIa, and IIb), required as intermediates, were obtained initially by a thermally promoted reaction of the appropriate vinylpyridine with ethyl diazoacetate, essentially according to the procedure used by Burger and associates for preparation of the 2 isomer IIa.[5] These products were each presumed *a priori* to consist predominantly of the *trans* isomer mixed with some of the *cis*, in view of the strong evidence elaborated in support of this conclusion for the analogous reactions with styrene[5,6] and with 2-vinylpyridine[7] (also *vide infra*). The isomers of II, which was subjected to more detailed analysis, were cleanly separated by gas chromatography, and the major component with the longer retention time was considered to be the *trans*. Hydrolysis under relatively moderate aqueous acid conditions afforded two isomeric carboxylic acids, XI and XII; the *trans* configuration was tentatively assigned to the principal product, XI.



II, 4 isomer; R = H; CX = $-COOC_2H_5$
IIa, 2 isomer; R = H; CX = $-COOC_2H_5$
IIb, 5 isomer; R = CH_3; CX = $-COOC_2H_5$
IIc, *trans*-4 isomer; R = H; CX = $-COOCH_3$
IId, 4 isomer; R = H; CX = $-CN$
XI, *trans*-4 isomer; R = H; CX = $-COOH$
XII, *cis*-4 isomer; R = H; CX = $-COOH$

Although the reaction of ethyl diazoacetate with styrene has been presumed to involve a carbene intermediate,[8] the reaction with the vinylpyridines, which proceeds under strictly comparable conditions, most probably involves primary addition of ethyl diazoacetate to the conjugated double bond in the same way as it ordinarily adds to α,β-unsaturated carbonyl compounds.[9] In fact, in line with the expectation that an electron-deficient carbene intermediate should react preferentially at the electron-rich nitrogen rather than at the electron-deficient vinylpyridine double bond, conditions calculated to generate a carbene (initial high temperature, ultraviolet light, copper catalysis[10]) afforded large quantities of water-soluble tars. The reaction of diazoacetic ester with 2-methyl-5-vinylpyridine, which is likewise considered to involve the molecular addition process, proceeds somewhat less vigorously and is more easily controlled than that with 2- or 4-vinylpyridine.

An alternative approach to desired 4-cyclopropylpyridine intermediates (II, IIc, and IId) was realized in the treatment of 4-picolyl chloride with sodium hydride and ethyl or methyl acrylate or acrylonitrile in a mixture of dimethylformamide and toluene. Reaction with the acrylates went smoothly in the cold (about 15°) to give 50–60% yields of II and IIc but become quite violent and produced large quantities of tars if the heat generated was not dissipated and the temperature was allowed to rise to about 30°. The more reactive acrylonitrile afforded IId in poor yield. The infrared spectrum of picolyl chloride derived II was essentially superimposable on that of II obtained *via* the diazoacetate route, thus confirming the gross structural assignment. The picolyl chloride process, however, proceeds somewhat more stereoselectively, and at least the ester products contain less *cis* material. Gas chromatographic analysis of fractionally distilled II obtained from the picolyl chloride process showed the presence of the two isomers in a ratio of 4:1. This proportion was corroborated by the n.m.r. spectrum of the distilled material, which at the same time clearly demonstrated that the major component was in fact the *trans* isomer, and the minor the *cis* isomer, a

---

[3] (a) Generically, cyprolidol. This compound is currently under clinical study. (b) We thank Dr. T. B. O'Dell and Mrs. M. D. Napoli for the pharmacological results and Dr. L. D. Miller for biochemical information.

[4] In our laboratories selected dogs showing aberrant behavior patterns that persist over several weeks of careful observation have been classified as "neurotic."

[5] A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *J. Am. Chem. Soc.*, **71**, 3307 (1949).

[6] A. Burger and W. L. Yost, *ibid.*, **70**, 2198 (1948); D. G. Markees and A. Burger, *ibid.*, **70**, 3329 (1948); also see E. N. Trachtenberg and G. Odian, *ibid.*, **80**, 4015 (1958).

[7] C. Kaiser, *et al.*, *J. Med. Pharm. Chem.*, **5**, 1243 (1962).

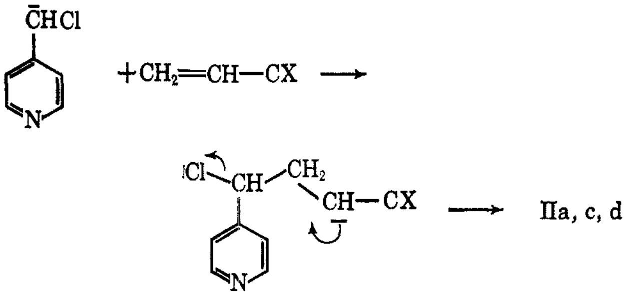
[8] W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p. 98.

[9] Since, during study of the thermally initiated reaction of ethyl diazoacetate with 4-vinylpyridine, nitrogen evolution was observed to take place in three distinct stages, it is tentatively suggested that three separate processes may be involved: *e.g.*, loss of nitrogen from the Δ^1-pyrazolines at 100–120°, and decomposition of the rearranged Δ^2-pyrazoline at 190°. No pyrazoline intermediates could be isolated. However, heating of reaction residues, after the product formed at temperatures up to 150° had been distilled out *in vacuo*, at 190° gave 5–10% more of II, identical with material produced at lower temperatures except that it appeared to be significantly richer in the *cis* isomer.

[10] It is recognized that the copper-catalyzed reaction most likely involves a copper–carbene complex: see P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, 443 (1961); K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *J. Am. Chem. Soc.*, **84**, 1015 (1962).

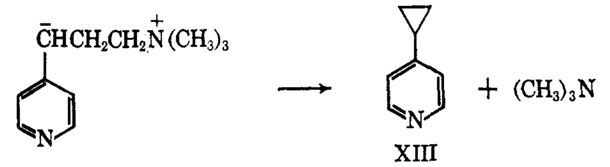
shielding effect in the *cis* compound causing an upfield shift in pattern for the protons of the ethyl group and a downfield shift for the pyridine ring protons.[11] The hydrochloride salt of picolyl chloride derived II formed colorless crystals which showed an analysis for a solvate, whereas that of the diazoacetate-derived product, although giving a correct analysis, could not be crystallized. The free base form of the methyl ester IIc crystallized after distillation; the n.m.r. spectrum of the recrystallized material, m.p. 42–43°, showed it to be the pure *trans* product.[11] (Subsequent reactions, discussed below, of the various preparations of II and IIc add further light.)

In this connection, mention should be made of McCoy's finding[12] that orientation in the analogous reaction of α-chloroacetate esters with acrylate esters using sodium hydride under comparable conditions is solvent determined and is stereoselectively *cis* in toluene and stereoselectively *trans* in dimethylformamide. Our reaction could not be effected satisfactorily in toluene[13] and was best carried out in a solvent mixture in which dimethylformamide was the major component. This reaction again probably does not involve a carbene intermediate[14] but rather addition of the picolyl chloride anion to the conjugated double bond, *viz.*



Attempts to effect the reverse condensation, *i.e.*, reaction of ethyl chloro- or bromoacetate or -malonate with 4-vinylpyridine, were abortive and yielded only products of self-condensation and/or tars.

Inasmuch as efforts to prepare the parent compound, 4-cyclopropylpyridine (XIII), by intramolecular cyclization of 4-chloropropylpyridine with base had met with little or no success, Bumgardner's report[15] that phenylpropyltrimethylammonium treated with sodamide furnished cyclopropylbenzene in excellent yield was of considerable interest. In accord with this, treatment of 4-pyridylpropyltrimethylammonium chloride with sodamide in tetrahydrofuran was found to provide XIII in close to 70% yield. The structural assignment was supported by the ultraviolet (*vide infra*) and infrared spectra of the product and by its lack of reaction with dilute permanganate in acid. Pertinent in this regard is the claim[16] to the synthesis of the isomeric 2-cyclopropylpyridine by catalytic hydrogenation of what was considered to be 2-cyclopropyl-6-chloropyridine. The refractive index reported by these authors for their product (1.511), however, contrasts sharply with that of XIII (1.542). These values, considered in conjunction with the refractive indices of 2- (1.547) and 4-vinylpyridine (1.549), styrene (1.546), 2- (1.503) and 4-picoline (1.506), toluene (1.496), and cyclopropylbenzene (1.533),[14] clearly show that the earlier workers could not have had 2-cyclopropylpyridine except as a component of a mixture, and it seems most probable that catalytic hydrogenation had caused appreciable cleavage of the cyclopropane ring.[17] Thus, the present report appears to offer the first successful synthesis of an unsubstituted cyclopropylpyridine system.



XIII

The compounds of ultimate interest (I and III–X) were prepared unexceptionally by action of the appropriate Grignard reagents on type-II intermediates. Side processes were minimized if the Grignard reactions were carried out at temperatures below 20°. Treatment of II derived from either the diazoacetate or picolyl chloride process, or of either the crude oil or pure crystalline solid form of the corresponding methyl ester IIc, with 2 equiv. of phenylmagnesium bromide afforded the same product, the *trans* isomer I, in about 50% yield.[18a] When II, originally prepared *via* the diazoacetate route but recovered from a previous reaction with 1 equiv. of phenylmagnesium bromide, was treated in the usual way with more of the Grignard reagent, 35% of I was obtained, but 8% of the *cis* isomer III could also be isolated.[18b] It is considered that, owing to steric hindrance, *cis* II adds the Grignard reagent more slowly than *trans* II and in consequence the recovered starting material was enriched in the *cis* isomer. The ultraviolet and infrared spectra of I and III accord with the proposition that the compounds differ only in configuration. The near-infrared spectrum of I reveals a strong C–H stretching overtone absorption at 1.675 μ (ϵ 1.9) suggestive of cyclopropane C–H.[19] Finally, the coupling patterns shown in the high-resolution (100-Mc.) n.m.r. spectra of I and III provided an independent confirmation of the configurational assignments.[20]

Reaction of diazoacetate-derived II with the sterically less demanding Grignard reagent, propylmagnesium bromide, furnished IV accompanied in this case

---

[11] We thank Dr. R. L. Hinman and Dr. E. Whipple of the Union Carbide Research Institute for this information.

[12] L. L. McCoy, *J. Am. Chem. Soc.*, **84**, 2246 (1962); *J. Org. Chem.*, **29**, 240 (1964).

[13] The difficulty here was that sodium hydride could not react fast enough with picolyl chloride in toluene so that self-quaternization supervened.

[14] See also W. Kirmse, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1 (1965).

[15] C. L. Bumgardner, *J. Am. Chem. Soc.*, **83**, 4420 (1961).

[16] R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *ibid.*, **70**, 1494 (1948).

[17] The reported melting point (115–117°) of the picrate of their product agrees exactly with that of 2-isopropylpyridine [W. Koenigs and G. Happe, *Ber.*, **35**, 1346 (1902)], and the melting points of other salts are not too much out of line. H. C. Brown and W. A. Murphey [*J. Am. Chem. Soc.*, **73**, 3308 (1951)] reported n_D 1.492 for 2-isopropylpyridine.

[18] (a) II obtained separately from the high-temperature treatment of diazoacetate residues[9] also yielded I. The fact that the various forms of II and IIc all gave the same Grignard product corroborates the thesis that these differ only in relative purity. (b) Small amounts of the *cis* isomer were also isolable when the reaction with diazoacetate-derived II was run on a large scale.

[19] *Cf.* P. G. Gassman, *Chem. Ind.* (London), 740 (1962); P. G. Gassman, D. H. Aue, and D. S. Patton, *J. Am. Chem. Soc.*, **86**, 4211 (1964); P. G. Gassman and W. M. Hooker, *ibid.*, **87**, 1079 (1965); H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964).

[20] We thank Dr. E. A. Pier of Varian Associates, Palo Alto, Calif., for obtaining and interpreting the n.m.r. spectra.

by a more significant quantity of its presumed *cis* isomer V. IIa, IIb, and IId, treated with phenylmagnesium bromide, and II, treated with *o*-tolyl- and cyclohexylmagnesium bromide, in each instance yielded a single isolated product; these were presumed to be the *trans* isomers, VIII, IX, X, VI, and VII, respectively.

After some earlier controversy, it has become quite firmly accepted that the modified π electrons of the cyclopropane ring can interact with attached π electron systems.[21] Of special interest in this regard are the ultraviolet absorption spectra of the present cyclopropylpyridine systems indicated in Table I. The spectral characteristics of 4-cyclopropylpyridine derivatives are particularly noteworthy. It can at once be seen that, whereas the 4-cyclopropylpyridine bases dissolved in 0.1 *N* sodium hydroxide show ultraviolet absorptions quite comparable with those of unconjugated, 4-substituted pyridine relatives (4-picoline, 4-benzylpyridine; contrast 4-phenylpyridine),[22] the cyclopropylpyridinium cation displays a markedly enhanced intensity of absorption associated with little shift in peak position. The spectral change is completely reversible. That the enhanced intensity of absorption is in fact ascribable to the cyclopropylpyridinium ion is clearly evidenced by the behavior of the methobromide salt of I, which shows the same spectrum and strong absorption band in the basic as well as in the acidic medium. These observations accord with other evidence that the cyclopropane ring is an electron-donating system.[21c,f] Further, these spectral properties have been found useful as a diagnostic tool, indicating the presence of the 4-cyclopropylpyridine system. The spectra of the carbalkoxy and cyano derivatives (II, IIc, and IId) in acid solution are somewhat more complex, suggestive of interaction with the carbonyl and cyano groups opposed to that with the charged pyridine ring.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compd.	λ_{max} (log ϵ), mμ — Base[b]	λ_{max} (log ϵ), mμ — Acid[c]
4-Substituted Pyridines		
4-Picoline	256 (3.26)	253.5 (3.59)
4-Benzylpyridine	258 (3.47)	254.5 (3.67)
4-Phenylpyridine	255 (4.2)[d]	284 (4.2)[d]
XIII	259 (3.38)	256.5 (4.11)
I	258 (3.44)	257 (4.21)
I methobromide	261 (4.25)	261 (4.24)
III	259 (3.29)	258 (4.07)
IV	258 (3.30)	258 (4.14)
V	259 (3.48)	261 (4.05)
VI	259 (3.58)	257.5 (4.17)
VII	258 (3.44)	262 (4.20)
IIc	259 (3.35)	243 (4.07) 255 (s) (4.01)
IId	260 (3.36)	237 (4.04) 255 (s) (3.87)
Other Substituted Pyridines		
Pyridine	257 (3.44)[e]	255.7 (3.72)[e]
2-Picoline	262 (3.55)[f]	262.5 (3.82)[f]
2-Phenylpyridine	241 (4.1)[d] 276 (4.0)	242 (3.9)[d] 295 (4.1)
3-Picoline	263 (3.49)[f]	262.5 (3.74)[f]
2,5-Lutidine	268 (3.6)[g]	268 (3.8)[g]
3-Phenylpyridine	246 (4.15)[d] 270s (3.8)	255 (4.0)[d] 295s (3.8)
VIII	270 (3.74)	278 (4.03)
IX	275.5 (3.62)	281 (3.79)

[a] Spectra were determined on a Bausch and Lomb Spectronic 505 recording spectrophotometer; absorption peaks were checked with a Beckman Model DU spectrophotometer. [b] Medium, 0.1 *N* sodium hydroxide in aqueous ethanol. [c] Medium, 0.1 *N* hydrochloric acid in aqueous ethanol. [d] P. Krumholz, *J. Am. Chem. Soc.*, **73,** 3487 (1951), as reported in "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 376. [e] *Ibid.*, Vol. II, H. E. Ungnade, Ed., 1960, p. 28. [f] *Ibid.*, p. 64. [g] *Ibid.*, p. 108.

As might have been anticipated (*cf.* the isomeric picolines and phenylpyridines), placing the cyclopropane ring at other pyridine positions results in different spectral shifts. The 2-cyclopropylpyridine derivative VIII, relative to 2-picoline, shows a much more moderate increase in intensity of absorption which, moreover, appears in the spectrum measured in basic as well as in acidic solution and which in both cases is accompanied by a significant bathochromic shift. On the other hand, compared with 2,5-lutidine, the 2-methyl-5-cyclopropyl derivative IX displays no enhancement of extinction coefficient in its spectrum run in either acid or base, but in both media does show a bathochromic shift of comparable magnitude. At the least, the spectral evidence indicates that the cyclopropane ring does take part in electron-orbital overlap with a pyridine ring.

The cyclopropylpyridine system offers a unique opportunity for evaluating ground-state electron-donating ability of the three-membered ring simply by measurements of basicity; the pK_a values of selected 4-substituted pyridine derivatives are listed in Table II. In particular, the parent compound, 4-cyclopropylpyridine (XIII), is significantly more basic than 4-picoline (or 4-isopropylpyridine), showing that, at least in the polarized and more demanding cationic form, ground-state orbital overlap by the cyclopropyl substituent acts to increase the electron density of the pyridine ring and thus to stabilize the protonated species. In light of this, the markedly reduced basicity of the carbethoxy derivative II is striking and must

TABLE II

DISSOCIATION CONSTANTS

Compd.	pK_a[a]	pK'_a[b]
4-Picoline	6.07[c]	5.71
XIII	6.44	5.99
VII		5.85
I	6.10	5.58
II	5.58	5.11

[a] Determined in water at 25° by measurement of ultraviolet absorption in 0.1 *N* HCl, in 0.1 *N* NaOH, and in acetate buffer solution. pH values were measured with a Heath-Malmstadt recording pH meter and are accurate to ±0.005 pH units. [b] Similarly determined in 25% ethanol. [c] H. C. Brown and X. R. Mihm [*J. Am. Chem. Soc.*, **77,** 1723 (1955)] reported a pK_a value of 6.02 for 4-picoline; 4-isopropylpyridine was also found to have a pK_a of 6.02.

---

[21] (a) W. W. Robertson, J. F. Music, and F. A. Matsen, *J. Am. Chem. Soc.*, **72**, 5260 (1950); (b) R. J. Mohrbacher and N. H. Cromwell, *ibid.*, **79**, 401 (1957); (c) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962), and references cited therein; R. Fuchs and J. J. Bloomfield, *ibid.*, **28**, 910 (1963); (d) M. Charton, *J. Chem. Soc.*, 1205 (1964); (e) A. L. Goodman and R. H. Eastman, *J. Am. Chem. Soc.*, **86**, 908 (1964); (f) L. A. Strait, R. Ketcham, D. Jambotkar, and V. P. Shah, *ibid.*, **86**, 4628 (1964).

[22] In base, the unconjugated compounds all show a broad complex of about three absorption bands centering at the tabulated wavelength.

reflect the competing demands made on the electrons of the cyclopropane ring by the protonated pyridyl and carbethoxy groups, although a field effect may contribute to the over-all base-weakening action. The fact that in water I is hardly more, and indeed in 25% ethanol is slightly less, basic than 4-picoline can be ascribed to inductive and/or field effects of the phenyl and hydroxy substituents, since replacing phenyl by cyclohexyl results in a distinctly more basic compound (VII).

In accord with other reports[21b,23] carbalkoxy-substituted cyclopropanes in the present series exhibit carbonyl stretching absorption bands in the infrared at lower frequencies than would be normal for saturated aliphatic carboxylic esters (see Table III). This is again indicative of π-orbital overlap with the cyclopropane ring. It may be noted that the carbonyl group of the hydrochloride salt of II absorbs at a slightly higher frequency than that of the free base, possibly suggestive of the opposing interaction of the cyclopropane ring with the pyridinium group. On the other hand, the carbonyl stretching bands of the hydrochloride salts of the free carboxylic acids XI and XII appear at perplexingly high frequencies. Particularly, the *trans* acid XI has an abnormally high-frequency carbonyl absorption. Further, the fact that the *trans* acid carbonyl absorbs at a considerably higher frequency than that of the *cis* isomer XII is not in line with the observation that *cis*-phenylcyclopropanecarboxylic acid absorbs at a slightly higher frequency than the *trans*.[21b] Of course, introduction of the protonated pyridine group, which could engage in hydrogen-bonding interaction with a *cis* carbonyl group, complicates the situation. Although, in line with the notorious susceptibility of the carbonyl stretching absorption of free carboxylic acids to medium effects, there is an appreciable shift in band position in going from potassium bromide disk to Nujol mull, the relative frequencies of absorption of the *cis* and *trans* acids are unaffected.

TABLE III

INFRARED CARBONYL STRETCHING FREQUENCIES[a]

Compd.	Form	Medium	$\nu_{\max}$, cm.$^{-1}$
II	Base	$CHCl_3$	1720
II	Hydrochloride	$CHCl_3$	1728
II	Hydrochloride	KBr disk	1725
IIc	Base	$CHCl_3$	1732
IIb	Base	CCl_4	1730
XI	Hydrochloride	KBr disk	1732
XI	Hydrochloride	Nujol mull	1720
XII	Hydrochloride	KBr disk	1712
XII	Hydrochloride	Nujol mull	1702

[a] Spectra measured with a Beckman IR-5 infrared spectrophotometer.

Experimental Section[24]

Reactions of Ethyl Diazoacetate with Vinylpyridines.—These were carried out essentially as described for the reaction with 2-vinylpyridine[5] either with or without solvent, although the reactions were moderated and proceeded more smoothly in a solvent (xylene). Temperature control was critical in either case. Conditions approaching optimum, based on a considerable background of experimentation, are given here.

A. **4-(2-Carbethoxycyclopropyl)pyridine (II). No Solvent.**—A mixture of 42.0 g. (0.4 mole) of 4-vinylpyridine and 45.6 g. (0.4 mole) of undistilled ethyl diazoacetate[25] was added, dropwise with stirring, to 21.0 g. (0.2 mole) of 4-vinylpyridine, preheated in an oil bath to 130–135° (pot temperature). The rate of addition was adjusted to maintain an internal temperature of 145 ± 5°, at which nitrogen evolution proceeded smoothly. After completion of the addition, stirring was continued and the reaction mixture was heated at a bath temperature of about 150° until nitrogen evolution essentially ceased (about 2 hr.). The reaction mixture was distilled, to the accompaniment of considerable further gas evolution, to give the crude product, boiling over the range 105–140° (2–3 mm.). An additional copious evolution of nitrogen and about 5–10% more material was obtained by raising the pot temperature to 190°. Redistillation afforded 37.0 g. (49%) of II as a colorless oil, boiling range 95–105° (0.3 mm.), 137–140° (4.5 mm.), n^{25}_{D} 1.5200.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: basic N, 7.27.

In Xylene.—To the ethyl diazoacetate obtained from 140 g. (1 mole) of ethyl glycinate hydrochloride in 200 ml. of xylene was added 105 g. (1 mole) of 4-vinylpyridine. The reaction mixture was heated, with stirring, to an internal temperature of 95° at which gas evoution proceeded vigorously and exothermically. The temperature was maintained at 100–103° by intermittent application of heat. After 30–40 min. the initial reaction had subsided and the temperature was slowly raised to 115–120°, at which point a second stage of rapid and exothermic evolution of gas took place. Afterwards the reaction mixture was heated at reflux for 5 hr. The ice-cooled mixture was extracted with dilute hydrochloric acid and the aqueous extract was made alkaline and extracted with benzene. Drying and removal of the benzene and distillation of the residue gave II, with identical properties and in comparable yield with that obtained in the absence of solvent.

The hydrochloride salt of II melted from 117 to 124° (gas evolution) after reprecipitation from isopropyl alcohol with ether.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20; Cl, 15.57. Found: C, 58.27; H, 6.29; ionic Cl, 15.17.

B. **2-(2-Carbethoxycyclopropyl)pyridine (IIa).**—Treatment of 2-vinylpyridine with ethyl diazoacetate furnished 30% of product, b.p. 121–123° (3.5 mm.), n^{23}_{D} 1.5166, picrate m.p. 118–120° (*cf.* Burger, *et al.*[5]).

C. **5-(2-Carbethoxycyclopropyl)-2-methylpyridine (IIb).**—Reaction of 2-methyl-5-vinylpyridine with ethyl diazoacetate in xylene, which proceeded less vigorously and which required less careful temperature control, yielded 43% of material, boiling range 102–112° (0.4 mm.), n^{24}_{D} 1.5170.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 69.96; H, 7.39; basic N, 6.79.

Reaction of 4-Picolyl Chloride with α,β-Unsaturated Carbonyl Compounds.—These reactions were carried out in a mixture of dimethylformamide and toluene. Again careful control of temperature was essential.

A. **4-(2-Carbethoxycyclopropyl)pyridine (II).**—A solution of 60 g. (0.6 mole) of ethyl acrylate and the 4-picolyl chloride from 49.2 g. (0.3 mole) of the hydrochloride salt[26] in 25 ml. of dry toluene was added, dropwise with stirring over a 45-min. period, to a slurry of 15.6 g. of a 47% oil dispersion of sodium hydride (0.3 mole) in 100 ml. of dry dimethylformamide maintained at 15–17° by cooling in an ice bath. After the addition was complete, the reaction mixture was stirred at 15–17° until heat and gas evolution ceased (about 3–4 hr.) and then allowed to come to room temperature. The reaction mixture was treated with a few milliliters of ethanol, diluted with 600 ml. of ether, and washed with a saturated aqueous sodium carbonate solution. The ether solution was extracted with dilute hydrochloric acid, the acid solution was made basic with sodium carbonate, and

---

[23] G. W. Cannon, A. A. Santilli, and P. Shenian, *J. Am. Chem. Soc.*, **81**, 1660 (1959).

[24] Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn., and the Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected. "Basic nitrogens" were determined by titration with acetous-perchloric acid, ionic halogens by potentiometric titration. All chemical shifts in the n.m.r. spectral data are given in parts per million downfield from tetramethylsilane, and coupling constants are in cycles per second.

[25] F. B. LaForge, W. A. Gersdorff, N. Green, and M. S. Schechter, *J. Org. Chem.*, **17**, 381 (1952).

[26] Aldrich Chemical Co.

the precipitated oil was taken into ether. Drying and evaporation of the ether solution and distillation of the residue gave 34.4 g. (60%) of II, boiling range 90–97° (0.2 mm.), $n^{24}\mathrm{D}$ 1.5205. Pertinent n.m.r. data for the mixture of isomers follow: major (80%) component (*trans*), α-pyridine ring proton, δ 8.37; β-proton, δ 6.93; ethyl CH_2, δ 4.12; CH_3, δ 1.23; minor (20%) component (*cis*), α-pyridine ring proton, δ 8.37; β-proton, δ 7.08; ethyl CH_2, δ 3.87; CH_3, δ 0.99.

Anal. Found: basic N, 7.23.

The hydrochloride salt of II, recrystallized from isopropyl alcohol–hexane, formed colorless crystals, m.p. 138–140° (gas evolution), apparently containing alcohol of crystallization. This may be the salt of the essentially pure *trans* isomer. Comparison of the infrared and ultraviolet absorption spectra of this product with those of the II obtained from the diazoacetate process showed no significant differences.

Anal. Calcd. for $C_{11}H_{14}ClNO_2 \cdot 0.25C_3H_8O$: C, 58.14; H, 6.64; Cl, 14.61. Found: C, 58.06; H, 6.68; ionic Cl, 14.40.

B. *trans*-4-(2-Carbomethoxycyclopropyl)pyridine (IIc).—Similar treatment of 4-picolyl chloride with methyl acrylate yielded 54% of product: boiling range 105–115° (2.5 mm.); $n^{26}\mathrm{D}$ 1.5295; crystallized from ether–hexane (Dry Ice bath), m.p. 42–43°; n.m.r. data, low-field cyclopropane ring proton, δ 2.39 (J = 4.5, 6.0, 9.0 c.p.s.).

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: basic N, 7.77.

C. 4-(2-Cyanocyclopropyl)pyridine (IId).—Similarly, reaction of 4-picolyl chloride with acrylonitrile afforded a poor yield, 18%, of material, boiling range 107–115° (0.3 mm.), $n^{24}\mathrm{D}$ 1.5524.

Anal. Calcd. for $C_9H_8N_2$: basic N, 9.72. Found: basic N, 9.44.

The hydrochloride salt formed colorless crystals from isopropyl alcohol–ether, m.p. 181–184°.

Anal. Calcd. for $C_9H_9ClN_2$: C, 59.84; H, 5.02; Cl, 19.63. Found: C, 59.55; H, 5.35; ionic Cl, 19.52.

Grignard Reactions.—These were performed in ether or, somewhat more conveniently, in tetrahydrofuran. Temperatures had to be kept low to avoid significant tar formation.

A. *trans*-2-(4-Pyridyl)-α,α-diphenylcyclopropanemethanol (I).—To a stirred solution of the Grignard reagent prepared from 236 g. (1.5 moles) of bromobenzene and 40.0 g. (1.65 g.-atoms) of magnesium shavings in 750 ml. of dried tetrahydrofuran, cooled in an ice bath to 10°, was added a solution of 114.7 g. (0.6 mole) of II in 600 ml. of tetrahydrofuran at a rate as rapid as was consonant with maintenance of the temperature at 10–12°. After the addition was complete, the reaction mixture was stirred for 30 min. and then allowed to warm to room temperature. The reaction mixture was poured into a saturated solution of ammonium chloride and ice. The tetrahydrofuran layer was separated and the aqueous layer was extracted several times with ether. The combined organic layers were concentrated *in vacuo* to a volume of about 350 ml., cooled in an ice bath, and acidified with a 5% aqueous solution of hydrochloric acid. The resultant precipitate of the crude hydrochloride salt of I was dissolved in methanol, and the methanol solution was made alkaline with dilute aqueous ammonia. The precipitated base was recrystallized from benzene–hexane to give 85.0 g. (47%) of I, m.p. 169–170°. Product having identical physical properties was obtained in comparable yield whether the starting material was II (derived from the diazoacetate or from the picolyl chloride process) or was the corresponding methyl ester, and whether the reaction was run in ether or tetrahydrofuran.

High-resolution (100-Mc.) n.m.r. data were geminal cyclopropane ring protons, δ 1.06 (J_{gem} = 4.9 c.p.s., J_{vic} = 5.0, 8.5 c.p.s.), δ 1.40 (J_{gem} = 4.9 c.p.s., J_{vic} = 6.2, 8.5 c.p.s.); remaining cyclopropane ring protons, complex multiplet centered at δ 2.0.

Anal. Calcd. for $C_{21}H_{19}NO$: N, 4.65. Found: basic N, 4.59.

The **hydrochloride salt** melted at 219–220° (gas evolution) after crystallization from methanol–ether.

Anal. Calcd. for $C_{21}H_{20}ClNO$: C, 74.65; H, 5.97; Cl, 10.50. Found: C, 74.82; H, 6.16; ionic Cl, 10.44.

The **methobromide salt**, recrystallized from isopropyl alcohol–hexane, showed m.p. 200–202°.

Anal. Calcd. for $C_{22}H_{22}BrNO$: C, 66.67; H, 5.60; Br, 20.17. Found: C, 66.22; H, 5.76; ionic Br, 20.03.

B. *trans*- and *cis*-2-(4-Pyridyl)-α,α-diphenylcyclopropanemethanol (I and III).—Similar treatment of II material (originally prepared by the diazoacetate process and recovered from a previous reaction with 1 equiv. of phenylmagnesium bromide) with more of the Grignard reagent in ether afforded 35% of the *trans* isomer I, m.p. 169–170°, mixture melting point undepressed. Recrystallization of the mother liquor material from benzene–hexane provided an 8% yield of the *cis* isomer III, m.p. 157–158°; a mixture of I and III melted at 141–148°.

High-resolution (100-Mc.) n.m.r. data were geminal cyclopropane ring protons, δ 1.10 (J_{gem} = 4.9 c.p.s., J_{vic} = 8.5, 8.5 c.p.s.), δ 1.65 (J_{gem} = 4.9 c.p.s., J_{vic} = 6.2, 6.2 c.p.s.); remaining cyclopropane ring protons, complex multiplet centered at δ 2.15.

Anal. Calcd. for $C_{21}H_{19}NO$: N, 4.65. Found (for III): basic N, 4.69.

The **hydrochloride salt of III** formed colorless crystals from isopropyl alcohol, m.p. 196° (gas evolution). The melting point of a mixture of the hydrochloride salts of I and III was depressed.

Anal. Calcd. for $C_{21}H_{20}ClNO$: C, 74.65; H, 5.97; Cl, 10.50. Found: C, 74.43; H, 6.02; ionic Cl, 10.45.

C. *trans*- and *cis*-2-(4-Pyridyl)-α,α-di-*n*-propylcyclopropanemethanol (IV and V).—An ether solution of 28.7 g. (0.15 mole) of II (from the diazoacetate process) was added, dropwise with stirring, to an ice-cold solution of the Grignard reagent from 44.3 g. (0.36 mole) of *n*-propyl bromide and 9.6 g. (0.4 g.-atom) of magnesium turnings in anhydrous ether. After being stirred for 1 hr. at ice-bath temperature, the reaction mixture was allowed to come to room temperature, washed with an aqueous solution of ammonium chloride, and extracted with dilute hydrochloric acid. The acid extract was made alkaline and extracted with ether. Drying and removal of the ether left an oil, which was crystallized from hexane to yield 5.8 g. (17%) of the *trans* product IV, m.p. 89–90°.

Anal. Calcd. for $C_{15}H_{23}NO$: N, 6.00. Found: basic N, 5.98.

The **hydrochloride salt of IV** melted at 154–154.5° (gas) after recrystallization from a mixture of isopropyl alcohol, ether, and hexane.

Anal. Calcd. for $C_{15}H_{24}ClNO$; C, 66.77; H, 8.97; Cl, 13.14. Found: C, 66.92; H, 9.05; ionic Cl, 13.17.

Crystallization of material obtained from the original hexane mother liquors from hexane provided 3.9 g. (11%) of the *cis* isomer V, m.p. 75–77°; the melting point was depressed on admixture with IV. The infrared and ultraviolet absorption spectra of IV and V supported the thesis that the compounds are configurational isomers.

Anal. Found: basic N, 5.97.

The **hydrochloride salt of V**, recrystallized from isopropyl alcohol–ether–hexane, showed m.p. 173° (gas evolution). A mixture melting point of the hydrochloride salts of IV and V was depressed.

Anal. Found: C, 66.83; H, 8.93; ionic Cl, 13.35.

D. *trans*-2-(4-Pyridyl)-α,α-bis(*o*-tolyl)cyclopropanemethanol (VI).—Similar treatment of II with *o*-tolylmagnesium bromide in ether gave VI, isolated in the form of the hydrochloride salt, m.p. 179° (gas evolution) after recrystallization from isopropyl alcohol–hexane.

Anal. Calcd. for $C_{23}H_{24}ClNO$: C, 75.50; H, 6.61; Cl, 9.69. Found: C, 75.43; H, 6.58; ionic Cl, 9.17.

E. *trans*-2-(4-Pyridyl)-α,α-dicyclohexylcyclopropanemethanol (VII).—Reaction of II with cyclohexylmagnesium chloride in ether yielded 30% of VII, m.p. 151–152° after recrystallization from benzene–hexane.

Anal. Calcd. for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.40; H, 9.98; basic N, 4.42.

The **hydrochloride salt**, recrystallized from isopropyl alcohol–ether and then from aqueous ethanol, melted sharply at 197° with gas evolution.

Anal. Calcd. for $C_{21}H_{32}ClNO$: Cl, 10.13. Found: Cl, 10.14, 10.18.

F. *trans*-2-(2-Pyridyl)-α,α-diphenylcyclopropanemethanol (VIII).—Similar treatment of 2-(2-carbethoxycyclopropyl)pyridine with phenylmagnesium bromide in ether gave 28% of VIII, m.p. 126–128° after recrystallization from hexane.

Anal. Calcd. for $C_{21}H_{19}NO$: N, 4.65. Found: basic N, 4.60.

The **hydrochloride salt of VIII**, recrystallized from ethanol–ether, showed m.p. 188–189° (gas evolution).

Anal. Calcd. for $C_{21}H_{20}ClNO$: C, 74.65; H, 5.97; Cl, 10.50. Found: C, 74.96; H, 5.85; ionic Cl, 10.48.

The **methobromide salt**, recrystallized from ethanol–ether, formed colorless crystals, m.p. 216–218°.

Anal. Calcd. for $C_{22}H_{22}BrNO$: C, 66.67; H, 5.60; Br, 20.17. Found: C, 66.96; H, 5.62; ionic Br, 20.05.

G. *trans*-2-(2-Methyl-5-pyridyl)-α,α-diphenylcyclopropanemethanol (IX).—Treatment of 5-(2-carbethoxycyclopropyl)-2-methylpyridine with phenylmagnesium bromide in ether and recrystallization of the crude product from benzene–hexane provided 26% of IX, m.p. 134–135°.

Anal. Calcd. for $C_{22}H_{21}NO$: N, 4.44. Found: basic N, 4.44.

The **hydrochloride salt of IX** formed colorless crystals, m.p. 190–191° (gas evolution) after recrystallization from a mixture of isopropyl alcohol, ether, and hexane.

Anal. Calcd. for $C_{22}H_{22}ClNO$: C, 75.09; H, 6.30; Cl, 10.08. Found: C, 74.57; H, 6.36; ionic Cl, 10.10.

H. *trans*-4-(2-Benzoylcyclopropyl)pyridine (X).—To a stirred solution, cooled in an ice bath, of the Grignard reagent prepared from 18.8 g. (0.12 mole) of bromobenzene and 3.1 g. (0.13 g.-atom) of magnesium in 75 ml. of anhydrous ether was added, dropwise, a solution of 14.4 g. (0.1 mole) of 4-(2-cyanocyclopropyl)pyridine in 50 ml. of ether. Stirring was continued for 2 hr. after the addition was complete. The reaction mixture was shaken with an aqueous solution of ammonium chloride and then extracted with dilute hydrochloric acid. The acid extract was made basic and extracted with ether, and the ether extract was dried and distilled to give a fraction, boiling range 144–160° (0.4 mm.), which solidified on standing. Recrystallization from hexane afforded 3.9 g. (17%) of X, m.p. 60–62°.

Anal. Calcd. for $C_{15}H_{13}NO$: N, 6.28. Found: basic N, 6.34.

The **hydrochloride salt of X**, recrystallized from isopropyl alcohol–ether, melted at 174–175°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; Cl, 13.65. Found: C, 68.83; H, 5.76; ionic Cl, 13.67.

***trans*- and *cis*-4-(2-Carboxycyclopropyl)pyridine (XI and XII).**—A solution of 15.0 g. (0.08 mole) of II (diazoacetate process) in 150 ml. of 6 *M* hydrochloric acid was heated for 4 hr. on a steam bath. Concentration of the solution *in vacuo* and recrystallization of the solid residue from methanol–ether gave 6.8 g. (44%) of the hydrochloride salt of what is considered to be the *trans* acid, m.p. 218° (gas evolution).

Anal. Calcd. for $C_9H_{10}ClNO_2$: Cl, 17.76; neut. equiv., 99.84. Found: ionic Cl, 17.61; neut. equiv., 102.9.

Evaporation of the crystallization mother liquors to dryness and recrystallization of the residue from isopropyl alcohol–ether and then from methanol–ether provided, after separation of additional *trans* material, 1.0 g. (6%) of the hydrochloride salt of the *cis* acid, m.p. 180–182° (gas evolution). A mixture melting point was depressed to 173°. Infrared and ultraviolet spectral examination support the supposition that the two acid products are configurational isomers.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.14; H, 5.05; Cl, 17.76. Found: C, 54.51; H, 5.66; ionic Cl, 17.77.

3-(4-Pyridyl)propyltrimethylammonium Chloride.—A solution of the 4-(3-chloropropyl)pyridine,[27] obtained from 147 g. (0.94 mole) of the hydrochloride salt, and 120 g. (2 moles) of trimethylamine in 600 ml. of acetonitrile was allowed to stand at room temperature in a stoppered flask for 14 days. After removal of about one-third of the solvent under reduced pressure, the solution was diluted with ether to precipitate an oil which was reprecipitated from isopropyl alcohol with ether. An isopropyl alcohol solution of this oil was treated with ethereal hydrogen chloride, and the resultant precipitate of the hydrochloride salt of the product was recrystallized from isopropyl alcohol to yield 166 g. (74%) of colorless crystals, m.p. 220–222°.

Anal. Calcd. for $C_{11}H_{20}Cl_2N_2$: C, 52.59; H, 8.03; Cl, 28.23. Found: C, 51.99; H, 8.16 ionic Cl, 28.28.

4-Cyclopropylpyridine (XIII).—To a stirred slurry of 52.0 g. (1.33 moles) of sodamide in a mixture of 1 l. of liquid ammonia and 500 ml. of tetrahydrofuran was added, portionwise, 166 g. (0.66 mole) of 3-(4-pyridyl)propyltrimethylammonium chloride hydrochloride. After replacement of the evaporated ammonia with 1 l. of additional tetrahydrofuran, stirring was continued and the reaction mixture was heated at reflux for 30 hr. The filtered reaction mixture was concentrated to dryness *in vacuo*, the residue was taken up in ether, and the ether solution was extracted with dilute hydrochloric acid. The acid extract was made alkaline and extracted with ether. Drying and removal of the ether and distillation of the residual oil yielded 53.0 g. (68%) of material, b.p. 72–73° (6 mm.), $n^{23}\text{D}$ 1.5425; the picrate, recrystallized from ethanol, showed m.p. 158–160°. An acid solution of the product did not effect rapid decolorization of dilute potassium permanganate. The refractive index and ultraviolet and infrared spectra of the material all accorded with the structural assignment.

Anal. Calcd. for C_8H_9N: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.46; H, 7.66; basic N, 11.63.

The **hydrochloride salt**, recrystallized from isopropyl alcohol–ether, showed m.p. 170–171°.

Anal. Calcd. for $C_8H_{10}ClN$: Cl, 22.78. Found: ionic Cl, 22.73.

Acknowledgments.—We thank Dr. L. Chafetz, Mr. D. F. Cortright, and Miss M. Unroe for analytical data and for infrared and ultraviolet spectral determinations. Larger scale runs carried out by Mr. E. Spinner afforded much significant information about the processes involved in the synthesis of I. We especially thank Dr. E. B. Whipple of the Union Carbide Research Institute for graciously providing and interpreting the n.m.r. spectral data, Professors N. J. Leonard and E. E. Smissman for advice relating to n.m.r. spectroscopy, and Drs. Han Tai and R. M. Powers of the A. E. Staley Manufacturing Company for near-infrared spectra.

---

[27] K. C. Kennard and D. M. Burness, *J. Org. Chem.*, **24**, 464 (1959).