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Cyclopropylpyridines. Interaction with Acid and Hydrogen. The Synthesis of Cyclopropane "Ring-Opened" Analogs[1]

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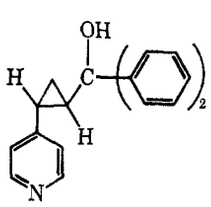
Under acid conditions, the cyclopropane ring of *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (I) cleaves to a relatively minor extent to give derivatives of 4-(4-pyridyl)-1,1-diphenyl-1-buten-4-ol accompanied by substantial amounts of recovered I. The relative resistance of I to acid is contrasted to the lability of analogs in which the pyridine ring has been reduced and of others in which the cyclopropane ring has been replaced by a saturated ethylene chain and is interpreted in terms of electronic interaction between the pyridinium and cyclopropane rings. The course of the reaction is suggestive of a concerted process. Catalytic hydrogenation of the methobromide salt of I gives the corresponding piperidine derivative without hydrogenolysis of the cyclopropane ring. Sodium borohydride reduction affords the related Δ^3-piperideine. Catalytic hydrogenation of the methobromide salts of other substituted cyclopropylpyridines is associated with concomitant hydrogenolysis of the cyclopropyl group giving straight propylene chain derivatives. Analogs of I in which the pyridine ring is replaced by a dimethylaminopropyl group and in which the cyclopropane ring is replaced by acetylenic and by *cis*- and *trans*-olefinic linkages have also been prepared. A useful synthesis of 4-ethynylpyridine has been devised.

The interesting pharmacological actions of *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (I) on the central nervous system[1,3] encouraged us to study the chemical properties of the pyridine–cyclopropane interacting system in greater detail. The preceding paper[1] advanced physical evidence [ultraviolet (uv), pK_a] in support of electronic interaction, particularly in the charged pyridinium cation. The present work considers implications of the behavior of I and certain of its



I

relatives when treated with acid and when subjected to conditions of catalytic hydrogenation. The effects of replacing the pyridine and cyclopropane rings with other moieties have also been investigated.

The effect of acid on cyclopropylcarbinols has been studied extensively following the classic paper of Roberts and Mazur;[4] the outcome depends on the structure of the reactants and on the reaction conditions. Treatment with strong acid usually effects cleavage of the cyclopropane ring smoothly in the cold,[4,5] although the action of acetic anhydride on appropriately substituted cyclopropylcarbinols can result in predominate formation of simple dehydration products accompanying products of ring cleavage.[6] The course of solvolytic reactions proceeding *via* cyclopropylcarbonium ions has been reviewed recently;[7,8] under kinetically controlled conditions unrearranged cyclopropyl, ring-expanded cyclobutyl[4,9] and ring cleavage products are generated in proportions apparently determined by the relative stabilities of the respective carbonium-ion canonical forms.[4,7,8,10]

Compound I proved to be comparatively resistant to acid treatment. When heated at 90–100° for 6 hr in 1 *N* sulfuric acid solution, 36% of I was recovered unchanged accompanied by 27% (based on recovered I) of the ring-cleaved product, 4-(4-pyridyl)-1,1-diphenyl-1-buten-4-ol (IIa) (eq 1), isolated as the hydrochloride salt. The structure of IIa was confirmed by its in-

(1) The preceding paper in this series: A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966).

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(3) L. Miller, M. Napoli, and T. B. O'Dell, *Arch. Intern. Pharmacodyn.*, **166**, 313 (1967).

(4) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951), and succeeding papers.

(5) See, *inter alia*, S. Julia, M. Julia, and L. Brasseur, *Bull. Soc. Chim. Fr.*, 1634 (1962); M. Hanack and H. Eggensperger, *Ann.*, **663**, 31 (1963); *Chem. Ber.*, **96**, 1259 (1963).

(6) *E.g.*, see S. Sarel, E. Breuer, Sh. Ertag, and R. Salamon, *Israel J. Chem.*, **1**, 451 (1963); S. K. Begidov, T. V. Domareva, and I. A. D'yakonov, *Zh. Obshch. Khim.*, **33**, 3426 (1963) [*Chem. Abstr.*, **60**, 5345 (1964)].

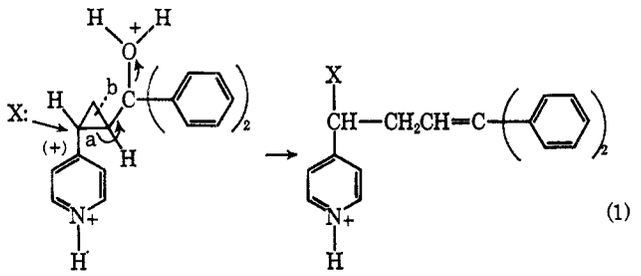
(7) M. Hanack and H. J. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **6**, 666 (1967); see especially pp 671, 672.

(8) Also see R. Breslow in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 259–273.

(9) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962).

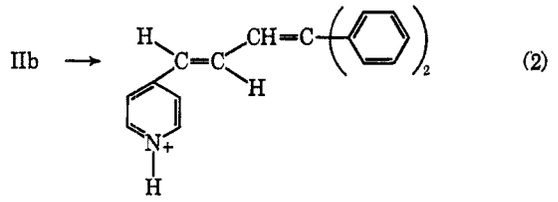
(10) *Cf.* P. von R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, **88**, 2321 (1966), and references cited therein.

frared (ir), nuclear magnetic resonance (nmr) (one double-bond proton absorbing as a triplet), and uv (Table I, diphenylethylene absorption, essentially unchanged in acid) spectra. In the course of the preparation of kilogram quantities of I hydrochloride required for clinical trials, ice-cold tetrahydrofuran–ether solutions of I were treated with cold, aqueous hydrochloric acid to precipitate the hydrochloride salt in good yield. When, however, combined mother liquors from several such runs were worked up, a small amount of the chloro analog of IIa (IIb) was obtained in the form of its hydrochloride salt, again showing diphenylethylene absorption in the ultraviolet (Table I). Heating IIb as the base to a bath temperature of 185° caused dehydrohalogenation and formation of the yellow hydrochloride salt of the butadiene derivative (III) (eq 2), structure



(1)

IIa, X = OH
b, X = Cl



(2)

III

confirmed by its ir, nmr, and uv (Table I, 1,1,4-triarylbutadiene, absorption, shifted in acid) spectra. The coupling constant of the multiplet ascribable to the acyclic double-bond protons in the nmr spectrum of III (J = 15 cps) suggests a *trans* configuration for the double bond adjacent to the pyridine ring.

The fact that bond a is cleaved rather than bond b and the direction of bond migration are of interest. Although the observed result could be rationalized in terms of thermodynamic rather than kinetic control, the course of the reaction is in accord with the idea of a concerted process, as shown in eq 1, without involvement of a carbonium-ion intermediate. Carbonium-ion formation from I with an already protonated pyridine ring, particularly if the electron-withdrawing effect is transmitted through the cyclopropyl group,[1] should be a rather high energy process and this is reflected in the relative stability of I under acid conditions. Certainly the carbon α to the pyridinium ring would be expected to bear very little of the positive charge in any generated carbonium ion and, consequently, II would not be an obvious product of a carbonium-ion reaction. On the other hand, the rate of a concerted displacement at the α carbon would be enhanced by the electronic interaction of the positively charge pyridine ring with an approaching nucleophile. In this connection it is worth noting that, although phenyl substitution on the carbinyl carbon markedly enhances the rate of a solvolytic process,[11] attachment of phenyl at the 2 position of the cyclopropane ring has little influence on rate.[12] Of course, the influence of a phenyl substituent on carbonium-ion stability may be somewhat equivocal[8] and certainly less clear than that of a pyridinium substituent.

TABLE I
ULTRAVIOLET ABSORPTION MAXIMA[a]

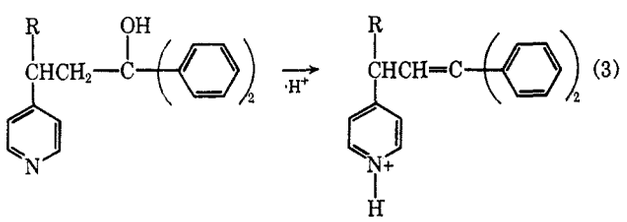
Compound	λ_{max} (log ϵ), mμ Base[b]	Acid[c]
I[d]	258 (3.44)	257 (4.21)
IIa	254 (4.14)	253 (4.21)
IIb	254 (4.17)	254 (4.18)
III	247 (4.22)	256 (4.19)
	340 (4.52)	384 (4.52)
IVa	255.5 (3.40)	252 (3.75)
IVb	257 (3.36)	...
Va	253 (4.24)	251 (4.27)
Vb	256 (4.21)	251 (4.23)
VIa	258.5 (2.70)	258 (2.69)[e]
VIb	258 (2.85)	258 (2.85)[f]
IX	252 (4.18)	251 (4.15)
XI	258.5 (2.62)	252 (4.28)[g]
XII	227 (4.22)	262 (4.04)
	260 (s) (3.78)	
XIII	253.5 (3.20)	253 (3.18)
XIV	248 (4.16)	273 (4.30)
XVa	253.5 (4.32)	281 (4.33)
XVb	245 (s) (4.00)	267 (4.00)
XVIa	257.5 (3.38)	254.5 (3.83)
XVIb	257.5 (3.40)	255 (3.79)
1,1-Diphenylethylene	250 (4.04)[h]	
1,1,3-Triphenylbutadiene	252 (4.20)[i]	
1,1,4-Triphenylbutadiene	240 (4.2)[j]	
	268 (3.7)	
	336 (4.6)	
1,1-Diphenylbutadiene	287 (4.37)[k]	
4-Vinylpyridine	242.5 (4.12)[l]	

[a] Spectra were determined with 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] See ref 1. [e] λ_{max} 251 mμ (log ϵ 4.07) after the acid solution had been allowed to stand for several hours. The neutralized solution showed λ_{max} 252 mμ (log ϵ 4.07). [f] Absorption when spectrum was determined immediately; after the solution had stood for 45 min at room temperature, λ_{max} 252 mμ (log ϵ 3.30). [g] Immediate reading; after the solution had been allowed to stand for 1 hr at room temperature, λ_{max} 252 mμ (log ϵ 4.81). [h] "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 557; solvent ethanol. [i] "Organic Electronic Spectral Data", Vol. III, O. H. Wheeler and L. A. Kaplan, Ed., 1966, p 860; solvent acetonitrile. [j] "Organic Electronic Spectral Data," Vol. II, H. E. Ungnade, Ed., 1960, p 687; solvent ethanol. [k] T. Holm, *Acta Chem. Scand.*, **17**, 2437 (1963); solvent cyclohexane. [l] Reference *h*, p 138; solvent ethanol.

The lability to acid of the formally "ring-opened" analogs of I, 3-(4-pyridyl)-1,1-diphenyl-1-propanol (IVa) and especially 3-(4-pyridyl)-1,1-diphenyl-1-butanol (IVb), synthesized by the methods indicated in the Experimental Section, may be contrasted to that of I. The hydrochloride salt of I could be prepared without difficulty under various conditions in protic or aprotic solvents. Although the hydrochloride salt of IVa could readily be prepared by treatment of an ice-cold benzene–chloroform solution of the base

(11) R. A. Sneen and A. C. Baron, *J. Amer. Chem. Soc.*, **83**, 614 (1961).
(12) R. A. Sneen, K. M. Lewandowski, I. A. I. Taha, and B. R. Smith, *ibid.*, **83**, 4843 (1961).

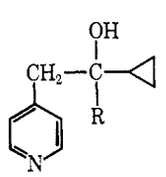
with ethereal hydrogen chloride and recrystallization of the precipitated salt from ethanol, treatment of an ice-cold methanol solution of the base with ethereal hydrogen chloride afforded isolated yields of 65% of IVa hydrochloride and 12% of the salt of the dehydrated product, 3-(4-pyridyl)-1,1-diphenyl-1-propene (Va). On the other hand IVb was so sensitive to acid that its hydrochloride salt could not be obtained under any conditions tried. Treatment of an ice-cold chloroform solution of IVb with ethereal hydrogen chloride yielded 75% of the corresponding dehydrated product (Vb) as the sole isolated product. Not too much can be made of these observations, particularly since acid treatment of IVa and IVb involves simple dehydration with loss of a proton (eq 3), whereas that of I effects rearrangement with breaking of a carbon–carbon bond. The special instability of IVb, moreover, must reflect steric crowding by the methyl substituent which, though apparently slight, is enough to throw the balance over to the side of dehydration. Nevertheless, it is tempting to think about the possibility that the site of carbonium-ion formation in IVa and IVb may be more effectively insulated from the charged pyridinium ring. (Clearer support for this hypothesis is gained from a comparison with derivatives in which the pyridine ring has been reduced, *vide infra*.)



IVa, R = H
b, R = CH_3

Va
b

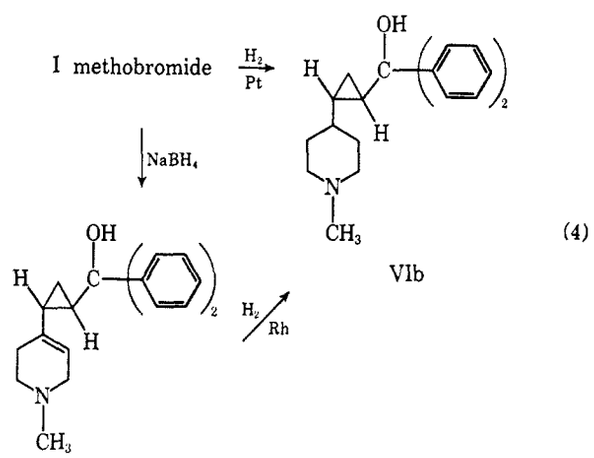
Although perhaps not directly pertinent to this discussion, it is of interest that α,α-dicyclopropyl-4-pyridineethanol (XVIa) and α-cyclopropyl-α-phenyl-4-pyridineethanol (XVIb), in which the carbinol carbon is closer to the pyridine ring, were not unusually unstable to acid.



XVIa, R = cyclopropyl
b, R = phenyl

Platinum-catalyzed hydrogenolysis of monoalkyl-substituted cyclopropanes, possibly proceeding *in part via* hydrogenation of a ring-opened intermediate,[13] occurs under mild conditions at room temperature and leads predominantly to branched-chain derivatives (hydrogenolysis of the unsubstituted, unhindered, carbon–carbon bond) accompanied by minor amounts of straight-chain products.[13,14] Ease of palladium-catalyzed hydrogenolysis of phenyl-substituted cyclopropanes decreases in the following order: *trans*-1,2-diphenyl- > phenyl- > *cis*-1,2-diphenyl- > 1,1-diphenylcyclopropane (the last was not hydrogenolyzed under the reaction conditions).[15] Phenylcyclopropanes are cleaved at the more substituted carbon–carbon bond and generally are hydrogenolyzed more readily than alkylcyclopropanes. The results have been explained in terms of conjugative effects.[15,16]

In view of these data it is of interest that Adams platinum-catalyzed hydrogenation of the methobromide salt of I[1] led smoothly, and without any appreciable cleavage of the cyclopropane ring, to a reasonably good yield (61%) of the N-methylpiperidine derivative, VIb. The same product was readily obtained by sodium borohydride reduction of the methobromide salt to yield *trans*-2-[4-(1-methyl-Δ^3-piperideinyl)]-α,α-diphenylcyclopropanemethanol (VIa, the structure of which was confirmed by its ir and nmr spectra, the latter showing the retention of the cyclopropane ring attached protons) followed by rhodium-catalyzed hydrogenation of VIa (eq 4). In contrast, hydrogenation

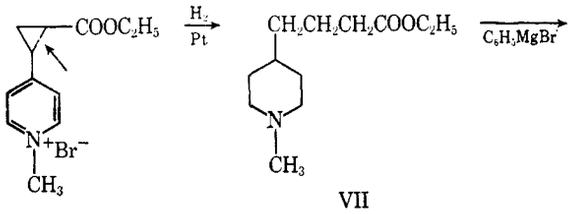


VIa

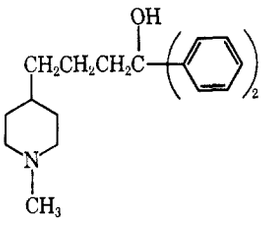
VIb

of the crude (predominantly *trans* but mixed with some of the *cis* isomer) methobromide salt of 4-(2-carbethoxycyclopropyl)pyridine[1] over Adams platinum oxide gave the cyclopropane ring cleaved, unbranched, ethyl γ-(1-methyl-4-piperidine)butyrate (VII) as the only isolable product. Treatment of VII with 2 equiv of phenylmagnesium bromide produced the diphenylcarbinol VIII (eq 5), the structure of which was confirmed by its ir and nmr spectra. A combination of decreased cyclopropane ring bond strength owing to opposing conjugative effects and decreased steric hindrance can serve to explain this observed hydrogenolysis. On the other hand, it is difficult to rationalize, on the basis of our earlier results and those reported in the literature,[16] our finding that the methobromide salt of 2-(4-pyridyl)-1,1-diphenycyclopropane (XII), prepared by reaction of 4-vinylpyridine with diphenyldiazomethane (see the Experimental Section for comments on this synthesis), was hydrogenolyzed over platinum oxide to give 3-(1-methyl-4-piperidyl)-1,1-diphenylpropane (XIII) as the only isolated product (eq 6), the structure of which was confirmed by spectral data. It is worth noting, however, that in both instances hydrogenolysis involves the most substituted

(13) M. Yu. Lukina, *Russ. Chem. Rev.*, **31**, 419 (1962); see pp 427, 428.
(14) See J. Newham and R. L. Burwell, Jr., *J. Phys. Chem.*, **66**, 1431 (1962), and references cited therein.
(15) B. A. Kazanskii, M. Yu. Lukina, and I. L. Safonova, *Dokl. Akad. Nauk SSSR*, **130**, 322 (1960) [*Chem. Abstr.*, **54**, 10953 (1960)].
(16) See ref 13, pp 435, 436.

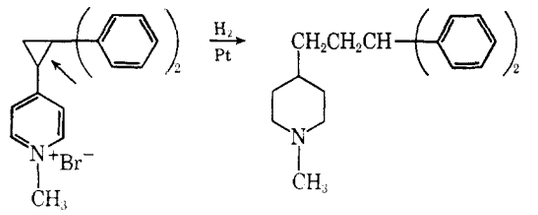


VII



(5)

VIII



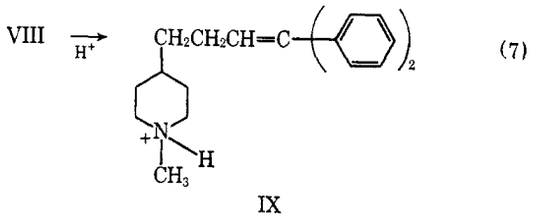
(6)

XII methobromide XIII

carbon–carbon bond. The difference in behavior of the methobromide salts of I and XII may possibly be ascribed to steric interaction in the salt of XII, which slows hydrogenation of the pyridinium group enough to allow hydrogenolysis to precede reduction. When hydrogenation of the pyridinium ring occurs first (as does happen with the salt of I) the cyclopropyl group is left unconjugated and therefore presumably more resistant to hydrogenolytic cleavage.[16a]

It is particularly useful to contrast the acid lability of VIa and VIb to that of I inasmuch as the partial or complete saturation of the pyridine ring in VIa and VIb eliminates orbital overlap between the π electrons of the pyridinium ring and the cyclopropane ring electrons as a possible cause of resistance to carbonium-ion formation. In support of this concept, VIa and VIb were found to be much more sensitive to acid than I. VIa could be titrated with acetous–perchloric acid and could be converted into a reasonably stable hydrochloride salt. However, whereas the ultraviolet absorption spectrum of I in 0.1 *N* hydrochloric acid showed no change after storage of the solution for up to 1 week at room temperature and the spectral shift in going from basic to acid solution was completely reversible,[1] the spectrum of VIa in 0.1 *N* hydrochloric acid changed quite rapidly from that of a simple benzene derivative to one reminiscent of a diphenylethylene in a matter of hours and this change was irreversible (Table I, see footnote *e*). The saturated compound VIb was especially sensitive to acid. Compound VIb could not be titrated with acetous–perchloric acid, giving evidence of decomposition during the titration, and could not be converted into a hydrochloride salt; the ultraviolet absorption spectrum of VIb in 0.1 *N* hydrochloric acid started undergoing irreversible change immediately on dissolution of the compound (Table I, see footnote *f*).[17]

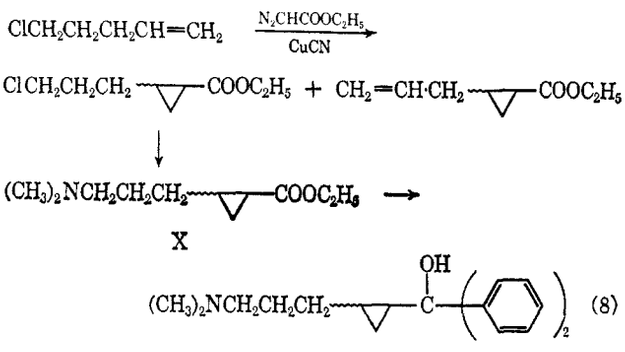
It should be noted that the cyclopropane ring opened compound VIII also proved to be significantly more labile to acid than its approximate (one methylene group less) pyridine counterpart IVa. Compound VIII could be titrated with acetous–perchloric acid and its hydrochloride salt could be prepared by careful treatment of a cold chloroform solution of the base with ethereal hydrogen chloride. Use of a slight excess of hydrogen chloride under the same conditions effected essentially quantitative dehydration of the material to give the hydrochloride salt of 4-(1-methyl-4-piperidyl)-1,1-diphenyl-1-butene (IX) (eq 7).



(7)

IX

In order to ascertain the effect of replacing the pyridine ring of I by a dimethylaminopropyl group, 5-chloro-1-pentene was heated with ethyl diazoacetate in the presence of cuprous cyanide to give ethyl 2-(3-chloropropyl)cyclopropanecarboxylate in low yield and accompanied by its dehydrohalogenated derivative. Treatment of the chloro compound with dimethylamine afforded ethyl 2-(3-dimethylaminopropyl)cyclopropanecarboxylate (X) which reacted with phenylmagnesium bromide to yield the desired 2-(3-dimethylaminopropyl)-α,α-diphenylcyclopropanemethanol (XI, configuration not established) (eq 8). It was intriguing



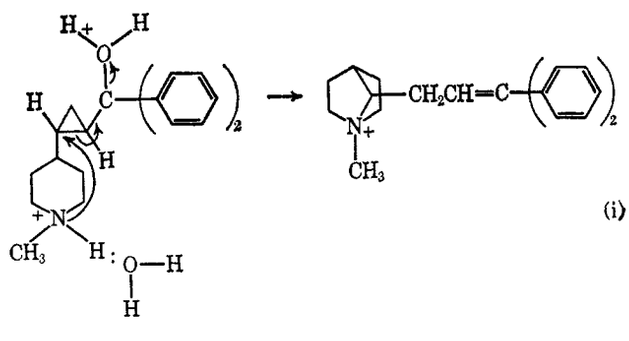
(8)

X

XI

(16a) NOTE ADDED IN PROOF.—A recent communication, W. J. Irwin and F. J. McQuillin, *Tetrahedron Lett.*, 2195 (1968), provides additional supportive evidence in regard to the influence of electrophilic conjugation on the direction and rate of hydrogenolysis of the cyclopropyl group, compares platinum *vs.* palladium as hydrogenolytic catalysts, and offers a plausible rationale for the observed results.

(17) Unfortunately, since the products of acid treatments of VIa and VIb were not isolated, nothing definitive can be said about their structures. The special lability of VIb, however, entices one into speculating about the possible involvement of the basic nitrogen (in equilibrium with the protonated form) in the process, *e.g.* eq i.



(i)

to find that XI, with its basic nitrogen the same number of carbon atoms away from the cyclopropyl group, was at least as sensitive to acid as VIb and behaved toward acid in strictly comparable fashion, although the extremely high extinction coefficient at 252 mμ developed by a solution of XI in 0.1 *N* hydrochloric acid after 1 hr at room temperature is not readily explicable (Table I, see footnote *g*).[17]

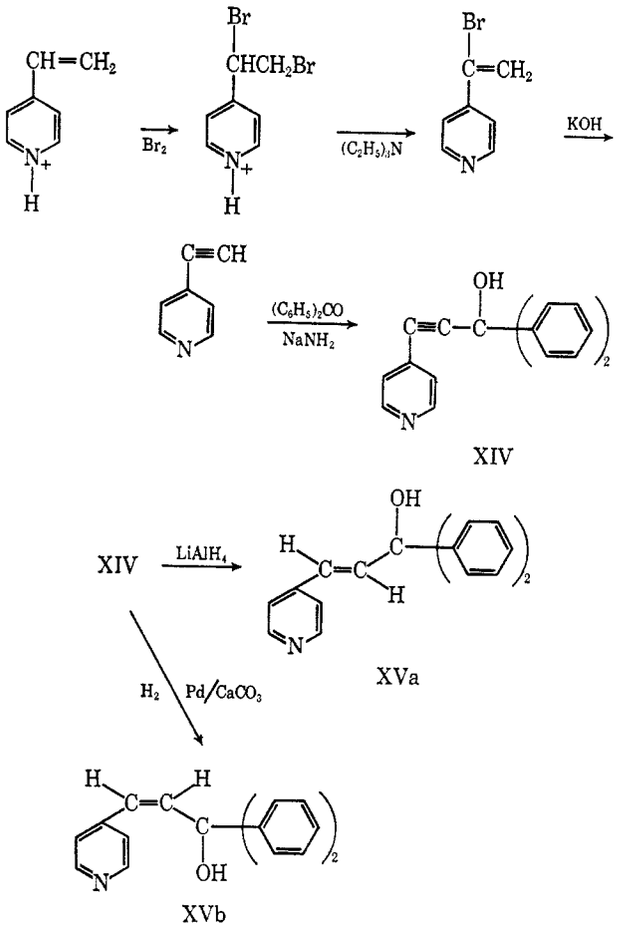
Analogs of I in which unsaturated groups replaced the cyclopropane ring were prepared from 4-ethynylpyridine since reactions of ethyl 4-pyridylacrylate with phenylmagnesium bromide or with phenyllithium afforded complex mixtures of 1,2- and 1,4-addition products.[18] To accomplish this end, a synthesis was developed which provided 4-ethynylpyridine in up to 29% yield from 4-vinylpyridine hydrochloride, a considerably better yield than had previously been realized (see pertinent references cited in the Experimental Section). The key was simply a two-step dehydrohalogenation of 4-vinylpyridine dibromide involving initial treatment of the dibromide with triethylamine under mild conditions followed by harsh treatment of the monobromo product with fused potassium hydroxide, care being taken to ensure minimum contact time of the product with alkali. Reaction of the sodium salt of 4-ethynylpyridine with benzophenone afforded α,α-diphenyl-γ-(4-pyridine)propynol (XIV) in good yield. Lithium aluminum hydride reduction of XIV yielded *trans*-α,α-diphenyl-γ-(4-pyridine)propenol (XVa) (Scheme I); the expected[19] *trans* configuration was supported by the nmr spectrum of the product which showed a coupling constant of $J = 16$ cps for the protons attached to the double bond. The *cis* isomer XVb was prepared by catalytic hydrogenation of XIV over Lindlar's catalyst. Neither XVa or XVb showed any special acid lability.

Of the compounds reported, only VIa produced central effects in animals comparable with those of I,[1,3] but activity in this instance was associated with a significant peripheral anticholinergic action.

Experimental Section[20]

Effect of Acid on *trans*-2-(4-Pyridyl)-α,α-diphenylcyclopropanemethanol (I). A. 4-(4-Pyridyl)-1,1-diphenyl-1-buten-4-ol Hydrochloride (IIa).—A solution of 24.0 g (0.08 mol) of I[1] in a mixture of 500 ml of 1 *N* aqueous sulfuric acid and 50 ml of ethanol was heated on a steam bath for 6 hr. The cooled solution was made alkaline with aqueous ammonia and the precipitate was dissolved in benzene. The benzene solution was shaken with 3% aqueous hydrochloric acid and the precipitated hydrochloride salt was collected. Addition of dilute sodium hydroxide to a methanol solution of the only slightly water-soluble salt gave a precipitate which was taken into chloroform. Drying and removal of the chloroform and recrystallization from benzene–hexane afforded 8.7 g (36%) of recovered I, mp 168–169°; the mixture melting point was undepressed.

SCHEME I



Making the aqueous hydrochloric acid filtrate basic with sodium carbonate, extracting the alkaline mixture with chloroform and drying, and removal of the organic solvent left a residue in the form of a yellow oil. An ice-cold ether solution of the oil was treated with ethereal hydrogen chloride to give a precipitate which was recrystallized from ethanol–ether and then from isopropyl alcohol to yield 4.0 g (17%) of the hydrochloric salt of IIa: mp 216–217° (the melting point of a mixture with the hydrochloride salt of I was markedly depressed); ir, ν_{max} (KBr), 3320 (OH), 1633 and 1605 (pyridinium); nmr ((DMSO-d_6), multiplet centered at δ 7.27 (phenyl protons), triplet at 6.23 (single double-bond proton).

Anal. Calcd for $C_{21}H_{20}ClNO$: C, 74.65; H, 5.97; Cl, 10.50. Found: C, 75.21; H, 5.99; ionic Cl, 10.48.

B. 4-Chloro-4-(4-pyridyl)-1,1-diphenyl-1-butene Hydrochloride (IIb).—In the course of work-up of larger scale runs of the Grignard reaction used for the preparation of I,[1] concentrated, ice-cold tetrahydrofuran–ether solutions of I were treated with cold 5% aqueous hydrochloric acid to precipitate the I hydrochloride. Low melting, mother liquor fractions obtained from recrystallizations of the hydrochloride salt were pooled and dissolved in methanol and the methanol solution was made alkaline with aqueous sodium hydroxide. The resultant precipitate was taken into chloroform and the chloroform solution was dried and concentrated to give a residue which was extracted with cold hexane (the material insoluble in the hexane proved to be I, mp 169–170° after recrystallization). Concentration of the hexane solution left a residual oil which was dissolved in ether. Treatment of the ether solution with ethereal hydrogen chloride gave a yellow precipitate which was recrystallized from mixtures of isopropyl alcohol, ether, and hexane to give IIb hydrochloride as colorless crystals: mp 129–132°; ir, ν_{max} (KBr), OH stretching absorption absent, 1637 and 1592 (pyridinium).

Anal. Calcd for $C_{21}H_{19}Cl_2N$: C, 70.79; H, 5.37; Cl, 19.90; ionic Cl, 9.95. Found: C, 70.35; H, 5.81; Cl, 19.53; ionic Cl, 9.72.

C. 4-(4-Pyridyl)-1,1-diphenyl-1,3-butadiene Hydrochloride (III).—Heating of 14 g of crude IIb (oil) under vacuum at a bath temperature of 185° caused rapid gas evolution and the

(18) Unpublished work from this laboratory.

(19) See J. D. Chanley and H. Sobotka, *J. Amer. Chem. Soc.*, **71**, 4140 (1949); W. Oroshnik, G. Karmas, and A. D. Mebane, *ibid.*, **74**, 3807 (1952); E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954).

(20) Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Melting points are corrected. "Basic nitrogens" were determined by titration with acetous–perchloric acid, ionic halogens by potentiometric titration. Infrared spectra were determined with a Beckman Model IR-5 spectrophotometer; peak positions are given in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were determined with a Varian Model A-60; pertinent chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and coupling constants in cycles per second (cps).

formation of a yellow solid. Recrystallization of the solid from isopropyl alcohol afforded 4.4 g of the hydrochloride salt of III as yellow crystals: mp 229–230°; ir, ν_{max} (KBr), OH band absent, 1640 and 1593 (pyridinium); nmr ($CDCl_3$), singlet at δ 7.39 (phenyl protons), multiplet centered at 6.94 (J = 15 cps, double-bond protons).

Anal. Calcd for $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; Cl, 11.09. Found: C, 78.55; H, 5.74; ionic Cl, 11.00.

3-(4-Pyridyl)-1,1-diphenyl-1-propanol (IVa).—To a stirred solution of approximately 0.3 mol of phenylmagnesium bromide in 300 ml of ether, cooled in an ice bath, was added 12 g of crude methyl β-(4-pyridine)propionate[21] in 125 ml of dry ether. A vigorous reaction ensued. After the addition was complete, the reaction mixture was allowed to stand for 16 hr in the refrigerator and then poured with rapid stirring on a slurry of ice and 33 g of ammonium chloride. The ether layer was separated and the aqueous mixture was extracted with benzene. The combined benzene–ether solution was concentrated almost to dryness and diluted with hexane to precipitate a solid which was recrystallized from benzene to yield 6.4 g (30%) of IVa, mp 159–160°.

Anal. Calcd for $C_{20}H_{19}NO$: N, 4.83. Found: basic N, 4.76.

The **hydrochloride salt**, prepared by treatment of an ice-cold benzene–chloroform solution of IVa with ethereal hydrogen chloride and recrystallized from ethanol, showed mp 182–183° (gas evolution); ir, ν_{max} (KBr) 3340 (OH), 1630 and 1590 (pyridinium).

Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.70; H, 6.18; Cl, 10.88. Found: C, 73.89; H, 6.16; ionic Cl, 10.83.

3-(4-Pyridyl)-1,1-diphenyl-1-propene Hydrochloride (Va).—To an ice-cold solution of 396 g of IVa in 6 l. of methanol was added, slowly with stirring, 300 ml of ethereal hydrogen chloride. After the mixture was stirred for about 45 min at ice-bath temperature, it was diluted with ether to precipitate a combined total of 288 g (65%) of the hydrochloride salt of IVa, mp 179–180°. Concentration of the mother liquor to dryness, crystallization of the residual oil from ethanol, and recrystallization from isopropyl alcohol afforded 45.7 g (12%) of the hydrochloride salt of Va in the form of colorless crystals: mp 158–159.5°; ir, ν_{max} (KBr), OH band absent, 1628 and 1593 (pyridinium).

Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; Cl, 11.52. Found: C, 78.11; H, 5.84; ionic Cl, 11.56.

3-(4-Pyridyl)-1,1-diphenyl-1-butanol (IVb).—A slurry of 9.0 g (0.23 mol) of powdered sodium amide and 25.0 g (0.23 mol) of 4-ethylpyridine (Eastman) in approximately 350 ml of liquid ammonia was stirred for 30 min and then a mixture of 45.3 g (0.23 mol) of diphenylethylene oxide[22] in 150 ml of tetrahydrofuran was added in portions over a 30-min period. Stirring was continued and the evaporating ammonia was gradually replaced by tetrahydrofuran. After all of the ammonia had evaporated, the reaction mixture was heated at reflux for 5 hr. A small amount of isopropyl alcohol was added to the cooled reaction mixture, followed by the dropwise addition of 350 ml of water. The tetrahydrofuran layer was separated and the water layer was extracted with ether. The combined organic layers were extracted with 5% aqueous hydrochloric acid. The acid extract was made alkaline to precipitate a red oil which was taken into ether. Drying and removal of the ether left a residue which was washed with hexane and recrystallized from isopropyl alcohol to yield 34.9 g (50%) of IVb as colorless crystals: mp 141–142°; ir, ν_{max} (KBr), broad OH stretching absorption, 1600 (pyridine).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.14; H, 6.98; N, 4.62. Found: C, 83.29; H, 6.96; basic N, 4.52.

3-(4-Pyridyl)-1,1-diphenyl-1-butene Hydrochloride (Vb).—An ice-cold chloroform solution of 15.0 g of IVb was treated with ethereal hydrogen chloride and the acidified solution was diluted with more ether to precipitate an oil, which crystallized from a mixture of ethyl acetate, isopropyl alcohol, and ether, and was recrystallized from isopropyl alcohol–ether to give 11.8 g (75%) of Vb as colorless crystals, mp 162–164°. No other material could be isolated from mother liquors. After one additional recrystallization from isopropyl alcohol–ether, the material had mp 165–167°; ir, ν_{max} (KBr), OH band absent, 1625 and 1600 (pyridinium).

Anal. Calcd for $C_{21}H_{20}ClN$: C, 78.38; H, 6.26; Cl, 11.02. Found: C, 78.50; H, 6.57; ionic Cl, 10.97.

3-(4-Pyridyl)-1,1-diphenyl-1-propanol (IVa).—A solution of 290 g (3.1 mol) of 4-picoline in 500 ml of dry tetrahydrofuran was added, dropwise with stirring over a 45-min period, to a slurry of 125 g (3.2 mol) of powdered sodium amide in approximately 5 l. of liquid ammonia. After being stirred for an additional 2 hr, the reaction mixture was treated, dropwise over a 2.5-hr period, with a solution of 362 g (1.55 mol) of 2-chloro-1,1-diphenylethanol.[22] Stirring was continued, tetrahydrofuran was added to replace the evaporating ammonia, and finally the reaction mixture was heated at reflux for 2.5 hr. A small amount of isopropyl alcohol followed by 1500 ml of water was added to the cooled reaction mixture. The tetrahydrofuran layer was separated and the water layer was washed with ether. The combined tetrahydrofuran–ether layers were washed with water, dried, and evaporated to dryness. Crystallization of the residue gave 308 g (69%) of IVa, mp 157–159°, identical with the material obtained from methyl β-pyridinepropionate.

***trans*-2-[4-(1-Methyl-Δ^3-piperideinyl)]-α,α-diphenylcyclopropanemethanol (VIa).**—To a stirred solution of 32.6 g (0.082 mol) of the methobromide salt of I[1] in 150 ml of methanol was added 25 g (0.66 mol) of sodium borohydride dissolved in 150 ml of methanol at a rate sufficient to maintain gentle reflux. After the addition was complete, the solution was heated at reflux for 2 hr and concentrated, and the solid residue was taken up in water and exhaustively extracted with ether. Drying and removal of the ether and crystallization of the residue from benzene–hexane gave 22.6 g (86%) of VIa: mp 154–156°; mp 156–158° after further recrystallization.

Anal. Calcd for $C_{22}H_{25}NO$: N, 4.39. Found: basic N, 4.31.

The **hydrochloride salt of VIa**, prepared in ice-cold chloroform–ether and recrystallized from isopropyl alcohol–hexane, showed mp 188–189° (gas evolution); ir, ν_{max} (KBr), 3330 (OH), 1667 (double bond), 1597 (phenyl); pK'_a (80% Methyl Cellosolve) 7.83; nmr (DMSO-d_6), multiplet centered at δ 7.37 (phenyl protons), multiplet centered at 5.40 (single piperideine double-bond proton), singlet at 2.73 (N–CH_3 protons), complex multiplet at below 1.0 (cyclopropane protons).

Anal. Calcd for $C_{22}H_{26}ClNO$: C, 74.24; H, 7.36; Cl, 9.96; neut equiv, 355.9. Found: C, 74.05; H, 7.55; ionic Cl, 9.76; neut equiv, 361.

***trans*-2-(1-Methyl-4-piperidyl)-α,α-diphenylcyclopropanemethanol (VIb).** A.—Acetic acid was added dropwise to a suspension of 8 g (0.025 mol) of VIa in *ca.* 200 ml of ethanol until all of the material had dissolved. The solution was shaken with 2 g of 5% rhodium on carbon at 50 psi of hydrogen and room temperature in an Adams–Parr apparatus. The calculated amount of hydrogen was taken up in 10 min. Dilute, aqueous sodium hydroxide was added to the filtered solution to precipitate a solid which was recrystallized from heptane to yield 5.7 g (71%) of VIb: mp 155–156°; mp 158–159.5° after further recrystallization from heptane; ir, ν_{max} ($CHCl_3$), 3610 (OH), 1600 (phenyl); unstable in acid; titration with acetous–perchloric acid anomalous; hydrochloride salt could not be prepared.

Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.13; H, 8.55; N, 4.41.

B.—A solution of 16.0 g (0.04 mol) of the methobromide salt of I[1] in 200 ml of ethanol was shaken with 0.5 g of platinum oxide at room temperature under 50-psi hydrogen pressure in an Adams–Parr apparatus. The calculated amount of hydrogen was taken up in 1 hr. The filtered solution was concentrated to one-half its volume, dilute aqueous ammonia was added, and the resultant precipitate was dissolved in ether. Drying and removal of the ether and recrystallization of the solid residue from benzene–hexane afforded 7.8 g (61%) of VIb, identical with the product obtained by method A above.

Ethyl γ-(1-Methyl-4-piperidine)butyrate (VII).—A solution of 73.0 g (0.25 mol) of the crude methobromide salt of 4-(2-carbethoxycyclopropyl)pyridine[1] in 200 ml of 50% aqueous ethanol was hydrogenated over 1 g of platinum oxide at 50 psi and room temperature. Hydrogen uptake was complete in 4 hr. The filtered solution was concentrated, diluted with water and made alkaline with sodium carbonate. The oil that separated was dissolved in ether. Drying and removal of the ether and distillation of the residual oil yielded 41.0 g (78%) of VII: bp 116–118° (4.5 mm); $n^{22}D$ 1.4600; ir, ν_{max} (CCl_4) 1733 (ester carbonyl). This was probably a mixture of isomers in view of difficulties encountered in isolating pure derivatives from it.

Anal. Calcd for $C_{12}H_{23}NO_2$: N, 6.57. Found: basic N, 6.49.

The **hydrochloride salt of VII** showed mp 105–106° after recrystallization from ethyl acetate; repeated crystallization from ethyl acetate raised the melting point to 146–148°; the ir spectrum showed a band at ν_{max} ($CHCl_3$) 1721 (ester carbonyl).

(21) A. R. Katritzky, *J. Chem. Soc.*, 2581 (1955).

(22) H. E. Zaugg and R. J. Michaels, *J. Amer. Chem. Soc.*, **80**, 2770 (1958).

Anal. Calcd for $C_{12}H_{24}ClNO_2$: C, 57.70; H, 9.68; Cl, 14.20. Found: C, 57.64; H, 9.28; ionic Cl, 14.23.

4-(1-Methyl-4-piperidyl)-1,1-diphenyl-1-butanol (VIII).—To the Grignard reagent prepared from 37.7 g (0.24 mol) of bromobenzene and 7.2 g (0.3 g-atom) of magnesium in 250 ml of tetrahydrofuran was added, dropwise with stirring at ice-bath temperature, a solution of 21.1 g (0.01 mol) of crude VII in 200 ml of tetrahydrofuran. After addition was complete the reaction mixture was stirred at room temperature for 3 hr, a 20% solution of ammonium chloride was added, and the reaction mixture was extracted with ether. The ether solution was extracted with dilute hydrochloric acid, the acid solution was made basic, and the oil precipitate was extracted with ether. No characterizable product could be isolated from the oil residue obtained from the ether solution. A white solid which remained undissolved during the ether extraction was recrystallized from heptane to give 6.5 g (20%) of VIII as colorless crystals: mp 184–185°; ir, ν_{max} (KBr), broad absorption in OH stretching region, 1597 (phenyl); nmr (DMSO-d_6), multiplet centered at δ 7.33 (phenyl protons), 2.64 (N-CH_3 protons), C-CH_3 peak absent.

Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.89; H, 9.21; basic N, 4.28.

Ethereal hydrogen chloride was added dropwise to a chloroform solution of 3.0 g of VIII, cooled in an ice bath, to the point at which the solution proved acid to moist pH paper. Dilution of the solution with hexane afforded a precipitate which was recrystallized from isopropyl alcohol to give 2.0 g of the **hydrochloride salt of VIII** as colorless crystals, mp 203–204° (gas evolution).

Anal. Calcd for $C_{22}H_{30}ClNO$: Cl, 9.85. Found: Cl, 9.94; ionic Cl, 9.80.

4-(1-Methyl-4-piperidyl)-1,1-diphenyl-1-butene Hydrochloride (IX).—Dropwise addition of a slight excess of ethereal hydrogen chloride to an ice-cold chloroform solution of 3.0 g of VIII and dilution with ether gave a precipitate which was recrystallized from isopropyl alcohol–ether to yield 2.3 g of the **hydrochloride salt of IX** as colorless crystals: mp 210–211°, mixture melting ponit with the hydrochloride salt of VIII markedly depressed; ir, ν_{max} (KBr), OH band absent, 1595 (phenyl).

Anal. Calcd for $C_{22}H_{28}ClN$: C, 77.27; H, 8.25; Cl, 10.37. Found: C, 77.30; H, 7.82; Cl, 10.71.

Ethyl 2-(3-Dimethylaminopropyl)cyclopropanecarboxylate (X).

A.—A solution of approximately 1 mol of ethyl diazoacetate[1] in 775 ml of xylene was added, dropwise with stirring, to a mixture of 100 g (0.95 mol) of 5-chloro-1-pentene and 3.6 g of cuprous cyanide in 250 ml of xylene heated on a steam bath. The addition took 2 hr, during which a total of 27.2 l. of nitrogen was evolved. After being heated for 1 hr more, the mixture was allowed to cool and filtered and the filtrate was concentrated at atmospheric pressure to remove xylene and starting material. The residual oil was vacuum distilled and redistilled through a 28-in. Nester–Faust spinning-band column to give 33.4 g (18%) of impure ethyl 2-(3-chloropropyl)cyclopropanecarboxylate, bp 121–123° (16 mm), $n^{25}D$ 1.4566. A forerun, boiling range 80–110° (16 mm), $n^{25}D$ 1.435–1.440, was found to be low in chlorine and apparently was largely ethyl 2-(2-propenyl)cyclopropanecarboxylate: ir, ν_{max} ($CHCl_3$) 1725 (ester carbonyl), 1643 (double bond). A high boiling residue was not further characterized.

B.—A solution of 33.2 g (0.17 mol) of crude ethyl 2-(3-chloropropyl)cyclopropanecarboxylate and 40.1 g (0.88 mol) of anhydrous dimethylamine in 200 ml of benzene was heated with shaking at 65–70° for 50 hr in a stoppered Parr pressure bottle. A total of 12.1 g (88%) of crude dimethylamine hydrochloride was filtered from the cooled reaction mixture. The filtrate was extracted with cold 5% hydrochloric acid solution; the aqueous extract was made basic with potassium carbonate and extracted with ether. Drying and removal of the ether followed by distillation of the residual yellow oil afforded 24.8 g (72%) of X: bp 118–119° (13 mm); $n^{25}D$ 1.4451; ir, ν_{max} ($CHCl_3$) 1715 (ester carbonyl); nmr ($CDCl_3$), quartet centered at δ 4.15 (ethoxy CH_2), triplet at 1.27 (ethoxy CH_3), singlet at 2.90 [N-$(CH_3)_2$], complex multiplet centered at about 1.0 (cyclopropane protons).

Anal. Calcd for $C_{11}H_{21}NO_2$: N, 7.03. Found: basic N, 7.08.

The **cyclohexanesulfamate salt of X**, prepared in ether–isopropyl alcohol and recrystallized from ethyl acetate, showed mp 94–95°.

Anal. Calcd for $C_{17}H_{34}N_2O_5S$: C, 53.94; H, 9.05; S, 8.47. Found: C, 54.32; H, 9.13; Schöniger S, 8.52.

2-(3-Dimethylaminopropyl)-α,α-diphenylcyclopropanemethanol (XI).—To an ice-cold slurry of the Grignard reagent prepared from 55 g (0.35 mol) of bromobenzene and 8.9 g (0.36 g-atom) of magnesium turnings in 225 ml of dry tetrahydrofuran was added, dropwise with stirring, a solution of 18.0 g (0.09 mol) of X in 50 ml of tetrahydrofuran. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 hr. The reaction mixture was poured into 300 ml of saturated ammonium chloride solution and extracted with ether. The ether extract was dried and evaporated to a thick oil residue that solidified on standing. This was dissolved in ice-cold, dilute aqueous hydrochloric acid. The aqueous solution was washed with ether, made basic, and extracted with ether. Drying and removal of the ether left an oily solid which was crystallized from acetone and recrystallized from pentane to give 6.8 g (22%) of colorless crystals of XI: mp 90–92°; ir, ν_{max} ($CHCl_3$) 3300 (OH), 1600 (phenyl); nmr ($CDCl_3$), multiplet centered at δ 7.33 (phenyl protons), singlet at 2.11 [N-$(CH_3)_2$], complex multiplet at below 1.0 (cyclopropane protons); unstable to acid; titration with acetous perchloric acid anomalous; acid addition salt could not be prepared.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.50; H, 8.80; N, 4.53. Found: C, 81.47; H, 8.88; N, 4.71.

2-(4-Pyridyl)-1,1-diphenylcyclopropane Hydrochloride (XII).—A solution of 25.2 g (0.13 mol) of crude diphenyldiazomethane[23] and 14.7 g (0.14 mol) of 4-vinylpyridine in 150 ml of tetrahydrofuran was slowly warmed[24] to reflux and heated at reflux for 11 hr during which period nitrogen was slowly evolved. The cooled, dark solution was diluted with hexane and filtered from a small amount of precipitate; the filtrate was concentrated under vacuum to a small volume and diluted with ether. Extraction of the ether solution with 5% aqueous hydrochloric acid caused formation of a precipitate which was recrystallized from isopropyl alcohol to yield 29.4 g (73%) of the hydrochloride salt of XII in the form of colorless crystals: mp 237° dec; ir, ν_{max} ($CHCl_3$) 1633 and 1605 (pyridinium).

Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; Cl, 11.52. Found: C, 77.71; H, 5.77; ionic Cl, 11.51.

The **methobromide salt of XII**, prepared by treating an acetonitrile solution of the base (oil) with methyl bromide and recrystallized from isopropyl alcohol–ether, showed mp 226° dec.

Anal. Calcd for $C_{21}H_{20}BrN$: C, 68.85; H, 5.50; Br, 21.82. Found: C, 68.84; H, 5.56; ionic Br, 21.75.

3-(1-Methyl-4-piperidyl)-1,1-diphenylpropane Hydrochloride (XIII).—A solution of 16.1 g (0.044 mol) of the methobromide salt of XII in 250 ml of 90% ethanol was shaken with 0.5 g of platinum oxide in an Adams–Parr apparatus under a hydrogen pressure of 50 psi. The calculated amount of hydrogen was absorbed in 1.5 hr. The filtered solution was concentrated to a smaller volume, diluted with water, made alkaline, and extracted with ether. Drying and removal of the ether left an oil which could not be crystallized. A dry ether solution of the oil was treated with ethereal hydrogen chloride and the precipitate recrystallized twice from isopropyl alcohol–ether–hexane and then from ethyl acetate–ether to give 4.3 g (30%) of the hydrochloride salt of XIII: mp 173–174° (further recrystallization from ethyl acetate–ether raised the melting point to 177–178°); ir, ν_{max} ($CHCl_3$) 1600 (phenyl); nmr ($CDCl_3$), singlet at δ 7.27 (phenyl protons), triplet centered at 3.84 (diphenylmethyl CH), singlet at 2.73 (N-CH_3).

Anal. Calcd for $C_{21}H_{28}ClN$: C, 76.45; H, 8.55; Cl, 10.75. Found: C, 76.63; H, 8.53; ionic Cl, 10.73.

4-Ethynylpyridine.[25,26]—A solution of 116 g (0.82 mol) of 4-

(23) D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p 134.

(24) The same product was obtained when the reactants were allowed to stand at room temperature in ether solution for 3 days. When, however, diphenyldiazomethane was added to excess 4-vinylpyridine heated at 130° in the presence of copper powder, very little nitrogen was evolved and a product, which was not entirely freed from impurities but which probably was a 2-pyrazoline derivative, was isolated. This material was stable to heating at above 200°; decomposition and nitrogen evolution took place at higher temperatures but without formation of a characterizable product. It seems likely that in the presence of a large excess of 4-vinylpyridine base at the higher temperature rearrangement of the presumably initially formed 1-pyrazoline to a more stable 2-pyrazoline superseded loss of nitrogen.

(25) Procedure patterned after that used by D. Leaver, W. K. Gibson, and J. D. R. Vass [*J. Chem. Soc.*, 6053 (1963)] for preparation of 2-ethynylpyridine in 30% yield. Conditions had to be modified in order to obtain a comparable yield of the 4 isomer.

(26) U. Haug and H. Fürst [*Chem. Ber.*, **93**, 593 (1960)] report mp 94.5–95° for 4-ethynylpyridine prepared by another method in 3.9% yield.

vinylpyridine hydrochloride (mp 240–243°, prepared from freshly distilled 4-vinylpyridine) in 550 ml of chloroform was treated, dropwise with stirring and cooling in an ice bath, with 262 g (1.62 mol) of bromine. After all of the bromine had been added, the reaction mixture was stirred for 1 hr at ice-bath temperature and then for 1 hr at room temperature. The reaction mixture was diluted with ether and the precipitated orange oil was washed with ether and treated with 500 ml of acetone to yield 209 g of the crude salt of **4-vinylpyridine dibromide**, mp 148–150°.

A 60.2-g portion of the crude salt was treated with aqueous sodium carbonate and the resulting base was taken into ether. The yellow ether solution was dried over magnesium sulfate, concentrated to a volume of 350 ml, and treated with a solution of 22.2 g (0.22 mol) of triethylamine in 100 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 hr and at reflux for 1.5 hr, 21 g of precipitated triethylamine hydrobromide was filtered off, and the filtrate was concentrated at reduced pressure to 39 g of an amber oil, presumed to be crude 4-pyridyl-1-bromoethylene.

To an intimate mixture of 56 g (1 mol) of powdered potassium hydroxide and 50 g of paraffin (mp ~56°), magnetically stirred and heated in an oil bath at 160° under a reduced pressure of 200 mm, 36 g of the crude 4-pyridyl-1-bromoethylene was added in small portions through a dropping funnel. The pressure was held at 200 mm for 1–2 min after the addition of each portion and then slowly reduced to 4 mm as the product distilled out of the reaction mixture and was collected in a recovery flask in the form of colorless crystals. This process was repeated until all of the material had been added. Recrystallization of the distilled material from pentane afforded 5.0 g of **4-ethynylpyridine**, mp 95–97°.[26] The mother liquor was concentrated and the residue was again subjected to treatment with potassium hydroxide–paraffin to provide an additional 1.6 g of **4-ethynylpyridine**, mp 95–98°, for a total of 6.6 g, representing an over-all yield from 4-vinylpyridine hydrochloride of 29%.

α,α-Diphenyl-γ-(4-pyridine)propynol (XIV).—To a stirred slurry of 7.8 g (0.2 mol) of sodamide in 300 ml of liquid ammonia was added 19.0 g (0.185 mol) of 4-ethynylpyridine followed by 33.7 g (0.185 mol) of benzophenone in 100 ml of dry ether. The evaporating ammonia was replaced by a total of 800 ml of ether and the reaction mixture was allowed to warm to room temperature. After a small amount of isopropyl alcohol had been added, the reaction mixture was shaken with 2.5% aqueous hydrochloric acid to give a white precipitate which was suspended in dilute sodium carbonate solution and exhaustively extracted with a mixture of chloroform and ether. Drying and evaporation to dryness of the organic extract and recrystallization of the residue from benzene–pentane yielded 40.0 g (76%) of XIV as colorless plates, mp 187–188°.

Anal. Calcd for $C_{20}H_{15}NO$: N, 4.91. Found: basic N, 4.89.

The **methanesulfonate salt of XIV** formed colorless needles from a mixture of isopropyl alcohol, ether, and hexane: mp 164–165°; ir, ν_{max} (KBr) 3280 (broad OH band), 2235 (triple bond), 1638 and 1602 (pyridinium).

Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; S, 8.41. Found: C, 66.75; H, 5.03; Schöniger S, 8.39.

***trans*-α,α-Diphenyl-γ-(4-pyridine)propenol (XVa).**—A slurry of 1.48 g (0.039 mol) of lithium aluminum hydride in 250 ml of dry ether was added in small portions to a stirred mixture of 12.5 g (0.044 mol) of XIV in 200 ml of ether. After completion of the addition, the resulting orange reaction mixture was heated at reflux for 3 hr, allowed to cool to room temperature, and treated with 10 ml of ethyl acetate followed by 50 ml of water. The precipitated aluminum hydroxide was filtered off, the water layer was separated from the filtrate, and the ether layer was diluted with chloroform and dried over magnesium sulfate. Evaporation of the ether–chloroform solution to a smaller volume caused precipitation of XVa as a white solid: 5.3 g (42%); mp 178–179°, mp 178.5–180° after recrystallization from benzene–hexane. A mixture melting point with XIV showed a slight but definite depression.

Anal. Calcd for $C_{20}H_{17}NO$: N, 4.87. Found: basic N, 4.80.

The **methanesulfonate salt of XVa** formed fine, colorless needles from isopropyl alcohol–ether: mp 178° (gas evolution); ir, ν_{max} (KBr) 3310 (broad OH band), 1632 and 1604 (pyridinium); nmr (D_2O), singlet at δ 7.48 (phenyl protons), 7.08 and 6.83 (double-bond protons, J_{trans} = 16 cps).

Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; S, 8.36. Found: C, 65.96; H, 5.60; Schöniger S, 8.55.

***cis*-α,α-Diphenyl-γ-(4-pyridine)propenol (XVb).**—A solution of 15.4 g (0.054 mol) of XIV and 1.4 g of quinoline in 300 ml of methanol was hydrogenated over 1.4 g of freshly prepared palladium–calcium carbonate (Lindlar's catalyst)[27] at room temperature and atmospheric pressure.[28] The calculated volume of hydrogen was absorbed in 1 hr. Concentration of the filtered solution to dryness under vacuum and recrystallization of the solid residue from benzene–heptane and from benzene–pentane yielded 7.0 g (49%) of XVb, mp 141–143°. Further recrystallization gave colorless needles: mp 147–149°, melting point depressed on admixture with IVa; ir, ν_{max} (KBr) 3150 (broad OH band), 1642 (double bond), 1600 (pyridine).

Anal. Calcd for $C_{20}H_{17}NO$: N, 4.87. Found: basic N, 4.89.

It may be noted that a crystalline methanesulfonate but not a crystalline hydrochloride salt was obtainable from XVa; the reverse was true of XVb. The **hydrochloride salt of XVb**, recrystallized from ethanol–ether, showed mp 168–168.5°; ir, ν_{max} (KBr) 3350 (OH), 1630 and 1603 (pyridinium); nmr (DMSO-d_6), multiplet centered at δ 7.40 (phenyl protons), singlet at 6.93 (double-bond protons).

Anal. Calcd for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; Cl, 10.95. Found: C, 74.06; H, 5.54; ionic Cl, 10.97.

α,α-Dicyclopropyl-4-pyridineethanol (XVIa).—To a stirred slurry of 12.3 g (0.31 mol) of sodium amide in 400 ml of liquid ammonia was added 28.4 g (0.3 mol) of 4-picoline followed by the dropwise addition of a solution of 33.4 g (0.3 mol) of dicyclopropyl ketone (Aldrich) in 150 ml of dry ether. The evaporating ammonia was replaced by an additional 500 ml of ether. The resultant reaction mixture was stirred for 1 hr at room temperature and poured on cracked ice, the ether layer was separated, and the aqueous phase was extracted with fresh ether. The combined, dried ether solution was concentrated to dryness under vacuum and the residual oil was distilled to yield 20.4 g (34%) of XVIa as a colorless oil, bp 135–141° (0.2 mm), which crystallized on standing, mp 51–53°.

Anal. Calcd for $C_{13}H_{17}NO$: N, 6.89. Found: basic N, 6.88.

The **hydrochloride salt of XVIa**, prepared by careful treatment of a cold ether solution of the base with ethereal hydrogen chloride and recrystallized from acetonitrile, formed large colorless needles: mp 140–141°; ir, ν_{max} (KBr) 3340 (OH), 1630 and 1592 (pyridinium).

Anal. Calcd for $C_{13}H_{18}ClNO$: C, 65.10; H, 7.56; Cl, 14.78. Found: C, 65.33; H, 7.65; Cl, 14.79.

α-Cyclopropyl-α-phenyl-4-pyridineethanol (XVIb).—A similar reaction of 4-picoline with cyclopropyl phenyl ketone (Aldrich) and recrystallization of the crude, distilled product [boiling range 90–185° (0.1 mm)] from acetone–pentane yielded 7.95 g (19.5%) of XVIb, mp 98–99°.

Anal. Calcd for $C_{16}H_{17}NO$: N, 5.85. Found: basic N, 5.80.

The **hydrochloride salt of XVIb**, recrystallized from isopropyl alcohol, showed mp 189.5–190° (gas evolution); ir, ν_{max} (KBr) 3340 (OH), 1628 and 1600 (pyridinium).

Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; Cl, 12.86. Found: C, 69.20; H, 6.60; ionic Cl, 12.96.

Registry No.—I, 6529-62-0; IIa, 16898-00-3; IIa hydrochloride, 16898-01-4; IIb, 16898-02-5; IIb hydrochloride, 16898-03-6; III, 16898-20-7; III hydrochloride, 16898-04-7; IVa, 16898-05-8; IVa hydrochloride, 16898-06-9; IVb, 16898-07-0; Va, 16898-08-1; Va hydrochloride, 16898-09-2; Vb, 16898-10-5; Vb hydrochloride, 16898-11-6; VIa, 16898-12-7; VIa hydrochloride, 16898-13-8; VIb, 16898-14-9; VII, 16898-15-0; VII hydrochloride, 16898-16-1; VIII, 16898-17-2; VIII hydrochloride, 16898-21-8; IX, 16898-22-9; IX hydrochloride, 16898-18-3; X, 16898-19-4; X cyclohexanesulfamate, 16898-23-0; XI, 16897-65-7; XII, 16897-73-7; XII hydrochloride, 16915-91-6; XII methobromide, 16897-66-8; XIII, 16897-67-9; XIII hydrochloride, 16897-68-0; XIV, 16897-53-3; XIV methanesulfonate,

(27) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952). When palladium on charcoal was used, the saturated compound (IVa), identified by comparison with authentic material, was obtained.

(28) The hydrogenation could also be carried out in an Adams–Parr apparatus at 40 psi.

16897-54-4; XVa, 16897-55-5; XVa methanesulfonate, 16915-95-0; XVb, 16897-69-1; XVb hydrochloride, 16897-70-4; XVIa, 16897-71-5; XVIa hydrochloride, 16897-74-8; XVIb, 16897-75-9; XVIb hydrochloride, 16897-76-0; 4-ethynylpyridine, 2510-22-7.

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The Reaction of Amino Heterocycles with Reactive Esters. I. 2-Aminopyridines

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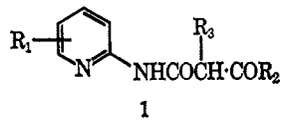
Very good yields of 4H-pyrido[1,2-*a*]pyrimidin-4-ones have been obtained in a one-stage synthesis by the condensation of 2-aminopyridines with β-keto esters or ethyl ethoxymethylenemalonate, and the corresponding 2,4-diones with diethyl malonate, in the presence of polyphosphoric acid (PPA). It is suggested that the cyclization of 2-acylacetamidopyridines with PPA to give pyrido[1,2-*a*]pyrimidin-4-ones involves the formation of N-(2-pyridyl)-β-(2′-pyridylamino)crotonamides since the latter on treatment with PPA give the same products.

It has recently been shown by Staskun and Israelstam[1] and Mallams and Israelstam[2] that hydroxyquinolines can be synthesized in one stage in good yields by heating arylamines with β-keto esters in the presence of PPA. This method avoids the necessity of following the two-stage method of Conrad and Limpach.[3-6] In an analogous way, we have now shown that pyrido[1,2-*a*]pyrimidin-4-ones can also easily be obtained in a one-stage process by condensing 2-aminopyridines with β-keto esters in the presence of PPA. The yields are much higher (in many cases 80% or more) than those obtained by other methods using a two-stage procedure involving the intermediate 2-acylacetamidopyridine (**1**) and its subsequent cyclization to the pyrido[1,2-*a*]pyrimidin-4-one (**2**).



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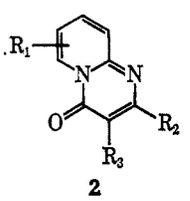

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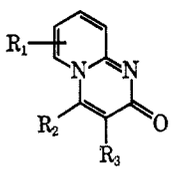
Optimum yields were obtained by heating 1 mol of the 2-aminopyridine with 1.5 mol of β-keto ester at 100° for about 1 hr together with a four- to sixfold quantity of PPA. Kato, *et al.*,[7] have obtained a 28% yield of 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one by treating 2-aminopyridine with diketene.

Table I gives some of the pyrido[1,2-*a*]pyrimidin-4-ones prepared, many of which are water soluble and pharmacologically active. 5-Nitro-2-aminopyridine failed to react.

Alkaline hydrolysis of these compounds yielded the 2-aminopyridines from which they were derived. This according to Lappin[8] proves that they were pyrido[1,2-*a*]pyrimidines and not 1,8-naphthyridines. Furthermore, oxidation yielded 4-hydroxypyrimidines.

Although some workers[9-14] considered that the base obtained from 2-aminopyridine and ethyl acetoacetate was 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3**, $R_1 = R_3 = H$; $R_2 = CH_3$), Antaki and Petrow[15]



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showed that the product was in fact the 2-methyl-4-keto isomer **2** ($R_1 = R_3 = H$; $R_2 = CH_3$) by virtue of its alternate synthesis from 2-bromopyridine and ethyl β-aminocrotonate.

The 4-keto structure was confirmed by Adams and Pachter[16] who converted 3-bromo-2-phenyl-4H-pyrido[1,2-*a*]pyrimidin-4-one into 2-phenylimidazo[1,2-*a*]pyridine.

However, further evidence has now been adduced not only in support of the 4-keto structure, but also of a possible mechanism for the reaction. Kucherov[13,14] has shown that, when N-(5-chloro-2-pyridyl)-β-(5′-chloro-2′-pyridylamino)crotonamide (**4**, $R_1 = R_4 =$ 5-Cl) is treated with sulfuric acid, a 7-chloropyrido[1,2-*a*]pyrimidinone was formed, which he incorrectly regarded as the 2-keto isomer.

It was therefore decided to investigate the products obtained by cyclization of unsymmetrical crotonamides (**4**) since the nature of these products would provide evidence both of the structure of the pyrimidinone and of a possible mechanism.

The conversion of the crotonamide into the pyrimidinone probably occurs in two stages: first, hydrolytic fission could occur at either bonds a or b with

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