

reflux under a nitrogen atmosphere for 3 hours. During the heating the organic portion gradually rose to the top of the molten formate as a dark-brown, hard layer. The reaction was allowed to cool, the contents of the test tube were digested first with water and then repeatedly with ethyl acetate to extract the organic component. All of the washings and extracts were poured into a separatory funnel, large volumes of water and ethyl acetate were added, and the dark brown reaction product shaken into solution. The ethyl acetate layer was washed twice with water, filtered through sodium sulfate, and evaporated to dryness *in vacuo* to give 75 mg. of a brown powder.

This crude amidation product was added to a mixture of 7.5 ml. of glacial acetic acid, 7.5 ml. of concd. HCl and 5 drops of water, and the solution refluxed for 50 minutes. The hot mixture was poured into water in a separatory funnel, the flask washed with ethyl acetate, and the washings combined with the diluted aqueous mixture. A large volume of ethyl acetate was added and the product isolated as above to give 44 mg. of an orange-brown solid. Repeated recrystallization from a small volume of dimethylformamide gave 7 mg. of orange-brown needles of the ( $\pm$ )-amide, dec. ca. 250°. The infrared spectrum, the ultraviolet spectrum (Fig. 3), biological activity toward *S. aureus*, and the chromatographic behavior<sup>47</sup> of this synthetic amide 38 were

(47) Chromatography was carried out on a column of Celite (registered trade-mark for diatomaceous silica produced by Johns-Manville Corp.) using the solvent system ethyl acetate-ethylene glycol-0.5% aqueous sodium carbonate (150:75:40).

identical with the corresponding properties of dextrorotatory amide 40 derived (*vide infra*) from the natural antibiotic 6-demethylchlorotetracycline.

(+)-Dedimethylamino-12a-deoxy-6-demethyl-anhydro-7-chlorotetracycline (40).—A solution of 3.75 g. of sodium acetate in 322 ml. of acetic acid and 138 ml. of water was stirred with nitrogen passing through, and 23 g. of 6-demethyl-7-chlorotetracycline hydrochloride was added. After a clear solution was obtained, zinc dust (27 g. total) was added in portions every hour for 7 hours. The excess zinc was then removed by filtration and the filtrate was added with stirring to 6 l. of 0.1 *N* hydrochloric acid. The precipitated dedimethylamino-12a-deoxy-6-demethyl-7-chlorotetracycline (39) was filtered, washed well with water and after drying weighed 15.5 g.

To a solution of 5 g. of this crude intermediate in 100 ml. of acetic acid was added 10 ml. of 31% hydrobromic acid in acetic acid, and the mixture was warmed at 60–70° for 20 minutes. After cooling, the dark reddish precipitate was filtered, washed with acetic acid, then ether, and dried (3.67 g.). This material was crystallized twice from dimethylformamide (first from 70 ml. and then from 40 ml.) and yielded 1.58 g. of pure product,  $[\alpha]_D^{25} + 1670^\circ$  (*c* 0.029 in dimethylformamide). The formation of different types of crystals during these crystallizations was shown to be related to the speed of cooling of the hot solution.

*Anal.* Calcd. for  $C_{19}H_{14}O_6ClN$ : C, 58.85; H, 3.64; N, 3.60; Cl, 9.15. Found: C, 59.15; H, 3.89; N, 3.87; Cl, 8.89.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

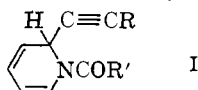
## Reaction of Silver Acetylide with Acylpyridinium Salts: N-Benzoyl-2-phenylethynyl-1,2-dihydropyridine<sup>1</sup>

BY TOSHIO AGAWA<sup>2</sup> AND SIDNEY I. MILLER

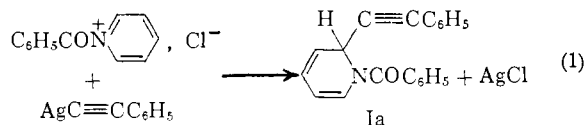
RECEIVED APRIL 7, 1960

The reaction between certain halides, pyridine and silver acetylides leads to the system N-acyl-2-alkynyl-1,2-dihydropyridine(I) as well as acylacetylenes as co-products. Basic hydrolysis of I gives the alkenylpyridines (III),  $RCH=CH(2-C_6H_4N)$ , while potassium hypobromite and possibly acid hydrolysis gives the alkynes,  $RC\equiv C(2-C_6H_4N)$ ; these constitute new paths to these unsaturated compounds. Reaction of the diene I with maleic anhydride leads to the isoquinuclidine system (2-azabicyclo[2.2.2]-7-octene) from which the azabicyclo[2.2.2]octadiene can be made.

We wish to report on a novel system



formed by nucleophilic attack on a pyridinium salt. Typically, the reaction is

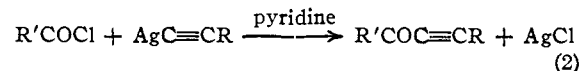


The product, N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (Ia), shows the properties of a diene, an amide, an alkyne and of an active hydrogen compound. Since there is no immediate precedent for 1, it is worthwhile to point out two other possible reaction paths.

Originally we hoped to exploit our finding that silver phenylacetylide is soluble in pyridine by effecting coupling reactions with halides, *e.g.*

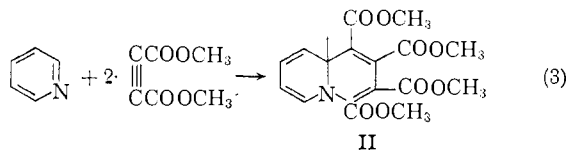
(1) Supported by the Air Force Office of Scientific Research under Contract No. AF 49 (638-39). Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Present address: Faculty of Engineering, Osaka University, Osaka, Japan.



Recently, Davis and Scheiber found that certain silver acetylides, *e.g.*, 1-butyl, were soluble and that others, *e.g.*, methyl or phenyl, were insoluble in carbon tetrachloride, chloroform and benzene.<sup>3</sup> In solution they found that these acetylides react according to 2, although in some instances aluminum chloride was a necessary co-reactant. In the present study we found that reaction 2 is a minor reaction path in the solvent pyridine, at least for the silver phenyl- or butylacetylides.

To account for the absence of 2, we first speculated that our reaction might be related to a curious one reported by Diels and Alder<sup>4</sup>



Attempts to effect a reaction between benzoyl-phenylacetylene or phenyl 1-hexynyl ketone and

(3) R. B. Davis and D. H. Scheiber, *THIS JOURNAL*, **78**, 1675 (1956).

(4) (a) O. Diels and K. Alder, *Ann.*, **498**, 16 (1932); **505**, 103 (1933);

(b) R. M. Acheson and G. A. Taylor, *Proc. Chem. Soc.*, 186 (1959).

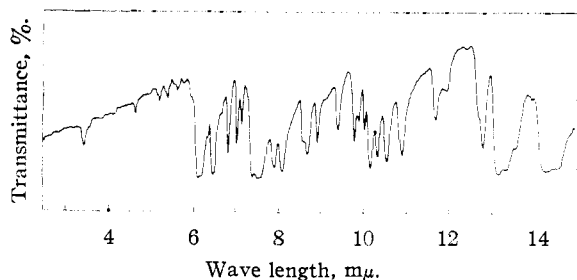
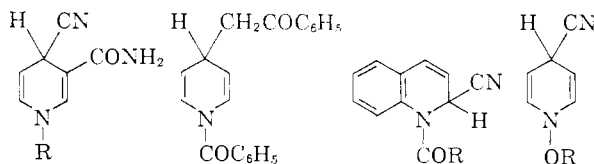


Fig. 1.—Infrared spectrum of N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (Ia) in a potassium bromide pellet.

pyridine under various conditions did not give Ia or analogs of II. Clearly, benzoylphenylacetylene was not an intermediate in the formation of Ia; at the same time, any possible similarity to 3 could be excluded.

Once the structure of I was established, it was not difficult to find mechanistic analogies in pyridine chemistry to render reaction 1 plausible. Now, silver acetylides are weak nucleophiles, *e.g.*, they do not react with *t*-butyl bromide or ketones.<sup>3</sup> But acylpyridinium salts are powerful electrophiles: nucleophilic attack at the acyl carbon as in reaction 2 is common<sup>5</sup>; nucleophilic attack at the 2- and 4-positions as in reaction 1 also has been reported *e.g.*<sup>5-9</sup>



Compounds of type I are certainly related to this group at least in their mode of formation.<sup>10</sup> Mech-

(5) R. H. Terres and W. E. McEwen, *THIS JOURNAL*, **76**, 580 (1954).

(6) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958).

(7) W. von E. Doering and W. E. McEwen, *THIS JOURNAL*, **73**, 2104 (1951); for analogous adducts between N-benzylpyridinium salts and methyl ketones, see F. Kröhnke, *et al.*, *Ann.*, **600**, 176, 211 (1956).

(8) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(9) W. E. Feely and E. M. Beavers, *THIS JOURNAL*, **81**, 4004 (1959).

(10) In reactions of this type specific orientation either to the 2- or the 4- position has been noted. Kosower has suggested that donors which form charge-transfer complexes from 1-methylpyridinium ions will substitute at the 4-position.<sup>11</sup> On the basis of various reports, it appears that this criterion is of limited applicability and cannot cover variations in the nucleophile, the heterocyclic system and the reaction conditions. Generally, nucleophiles attack the 4- position of acylpyridinium but the 2-position of acylquinolinium cation<sup>5,12</sup>; in our reaction 1, however, attack is at the 2-position of the pyridinium ion. For N-alkyl-3-acylsubstituted pyridinium ions or for N-alkyl-quinolinium ions attack favors the 4-position.<sup>13</sup> Heterocyclic N-oxides or their salts are attacked in either the 2- or 4- position<sup>14</sup> (recently this has led to the facile synthesis of 2-ethynylpyridine-N-oxide and 2-ethynylquinoline-N-oxide).<sup>15</sup> Finally, the reactions of pyridine and quinoline with amide ion, hydroxide ion and organometallics favor 2-substituted products.<sup>16,17</sup> These examples require that nucleophilic attack on pyridine species is sensitive to several possibly complex factors.

(11) E. M. Kosower and S. W. Bauer, *THIS JOURNAL*, **82**, 2191 (1960); **78**, 3497 (1956).

(12) W. E. McEwen, R. H. Terres and I. W. Elliott, *ibid.*, **74**, 3605 (1952).

(13) M. R. Lamborg, R. M. Burton and N. O. Kaplan, *ibid.*, **79**, 6173 (1957); A. Kaufmann and R. Widmer, *Ber.*, **44**, 2058 (1911).

(14) A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956).

(15) J. H. Blumenthal, U. S. Patent 2,874,162; *C. A.*, **53**, 12311 (1959).

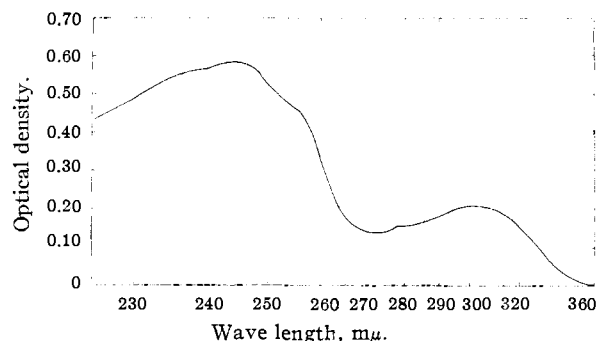
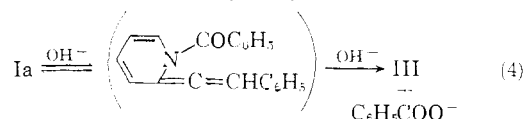


Fig. 2.—Ultraviolet spectrum of N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (Ia).

anistically we have the interesting net result that a carbonium ion, possibly assisted by chloride, has displaced silver ion.

### Results and Discussion

The key compound in the structure identification of Ia appeared to be III which was obtained from it in high yield by basic hydrolysis. The structure



of Ia was established on the basis of its elemental analysis, spectral evidence and its chemical transformations. Its infrared and ultraviolet spectra are given in Figs. 1 and 2. In concentrated solution in chloroform, the weak band at 2220 and the very strong band at 1665  $\text{cm}^{-1}$  are very probably the triple bond and amide carbonyl absorptions, respectively; the weak band at 2900 and the medium band at 1609  $\text{cm}^{-1}$  may be the tertiary carbon-hydrogen and diene frequencies, respectively.<sup>18</sup> Definite conclusions cannot be drawn from the ultraviolet spectrum of Ia (Fig. 2) except that it is consistent with that observed for a number of N-substituted dihydropyridines.<sup>19,20</sup>

The reactions of Ia are given in Chart 1. Chemically Ia is a neutral substance, water insoluble and inert to the usual amine reagents, *e.g.*, picric acid, methyl iodide or cold hydrogen chloride in benzene. By analogy with Reissert compounds (N-acyl-2-cyano-1,2-dihydroquinolines),<sup>8</sup> we expected acid treatment of Ia to yield benzaldehyde and IV (or its hydration product, 2-phenacylpyridine<sup>21</sup>). Although acid attack did lead to benzaldehyde, evidence for IV was lacking. The reaction of Ia with 2,4-dinitrophenylhydrazine reagent containing sulfuric acid did not lead to a DNP derived from IV; instead a 1:1 adduct resulted which may be an  $-\text{N}-\text{H}$  addition across the triple bond.

(16) H. S. Mosher, "Heterocyclic Compounds," R. C. Elderfield, editor, John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 8.

(17) A. E. Tchitchibabine, "Traité de Chimie Organique," V. Grignard, ed., Masson et Cie., Paris, France, 1953, Vol. XX, pp. 91 ff.

(18) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Chaps. 1-3, 12.

(19) D. Craig, L. Schaeffgen and W. P. Tyler, *THIS JOURNAL*, **70**, 1624 (1948).

(20) K. Wallenfels and M. Gellrich, *Ber.*, **92**, 1406 (1959).

(21) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929); H. C. Beyerman, W. Eveleens and Y. M. F. Muller, *Rec. trav. chim.*, **75**, 63 (1956).

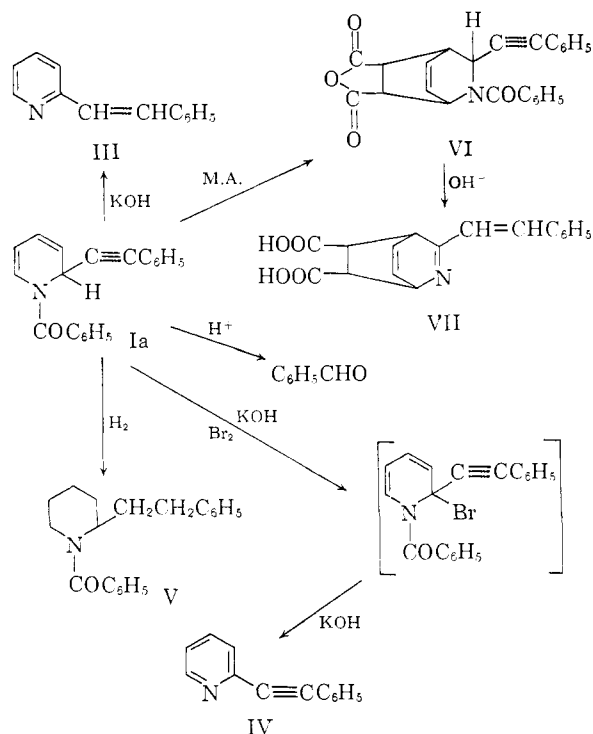
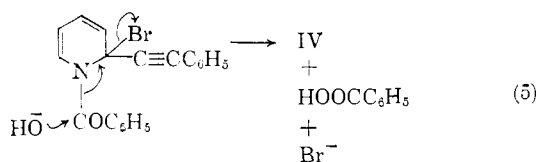


Chart 1.—Transformations of N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (M. A. = maleic anhydride).

The 2-substituted hydrogen of Ia, which is simultaneously allylic and propargylic, was assumed to be relatively acidic. In this way a plausible mechanism could be devised for the conversion of Ia to stilbazole (see 4). The lability of this hydrogen was indicated by its exchange with deuterium in deuterium oxide-triethylamine solution and by its replacement by bromine in cold hypobromite solution. The bromide was not purified; in basic solution it gave IV probably according to



As an unsaturated compound Ia absorbed four moles of hydrogen to give N-benzoyl-2-phenylethylpiperidine (V). Although Ia adds bromine rapidly, the products could not be purified. As a diene, Ia reacted with maleic anhydride to give the N-benzoyl-3-phenylethynyl-7,8-dicarboxyanhydride-2-azabicyclo[2.2.2]-7-octene (VI). Other dihydropyridines have previously been shown to give maleic anhydride adducts<sup>22</sup>; all of these, of course, are isoquinuclidines with one double bond.

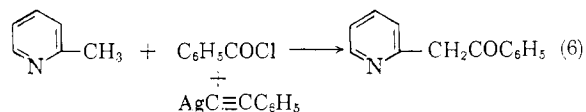
Compound VI, however, can easily be converted to VII by the process given in 4 whereby Ia was converted to 2-stilbazole (see Chart 1); VII is an azabicyclo[2.2.2]-2,7-octadiene. Its mode of formation suggests a possible route to azabicyclo-(2.2.2)octatrienes. Neither the dienes nor the trienes appear to have been reported previously.

(22) D. Craig, A. K. Kuder and J. Efromson, *THIS JOURNAL*, **72**, 5236 (1950); O. Mumm and J. Diederichsen, *Ann.*, **538**, 195 (1939).

We have treated Ia as a model system. Six other syntheses of I are given below. The structures have all tentatively been assigned to the 2- rather than the 4-substituted dihydropyridine. In some cases the product was converted with methanolic hydroxide as in 4 into the corresponding 2-alkenylpyridine.

The chemistry of other I analogs is not so well known. Attempted synthesis failed, not in the lack of reaction, but in the resolution of the dark and complex product mixtures. The "negative" reactants in pyridine were silver phenylacetylacetyl chloride, silver butylacetylacetyl chloride, silver butylacetylacetyl-*p*-nitrobenzoyl chloride and the silver salt of 1-ethynylcyclohexanol also with these three acid halides. Thus, more work is needed to establish the scope of synthesis 1.

The reaction between 2-picoline, benzoyl chloride and silver phenylacetylacetyl led to 2-phenacylpyridine, silver chloride and presumably phenylacetylene. This route to keto-picolines presum-



ably depends on the active methyl hydrogen,<sup>16, 17</sup> and may be capable of extension.

### Experimental

Melting and boiling points are uncorrected. Microanalyses are by Micro Tech Laboratories, Skokie, Ill. Infrared spectra were taken on a Perkin-Elmer Infracord or model 21 spectrophotometers. Ultraviolet spectra were measured on a Beckman DK spectrophotometer.

**Silver Acetylides.**—The acetylides were prepared by reaction of the alkyne with ammoniacal silver nitrate in methanol. The solid products were washed with methanol and vacuum dried. The solubility of silver phenylacetylacetyl in a wide variety of solvents was investigated briefly. This salt was soluble in pyridine to the extent of 0.162 g. per 3.20 g. pyridine at 24.8° (since the solution becomes turbid on standing, this is approximate); it is also soluble in 2-methylpyridine and in quinoline. The silver salts of 1-hexyne, 1-ethynylcyclohexanol and 3-phenylbutyn-3-ol were soluble but that of propargyl alcohol was not soluble in pyridine.<sup>23</sup>

These acetylides were separated from silver chloride by their solubility in nitric acid or the solubility of silver chloride in aqueous ammonia.

**Reactions of Ketoacetylenes with Pyridine.**—Phenyl 1-hexynyl ketone was prepared by the method of Davis and Sheiber.<sup>3</sup> It had b.p. 115–120° (0.7 mm.),  $n_D^{20}$  1.5438 (lit.<sup>3</sup> b.p. 101–102° (0.1 mm.),  $n_D^{20}$  1.5432) and a dinitrophenylhydrazone, m.p. 149–152° (lit.<sup>3</sup> m.p. 156–156.5°). Benzoylphenylacetylene was obtained as a co-product of Ia and also by the method of Nef.<sup>24</sup>

When phenyl 1-hexynyl ketone, pyridine and benzoyl chloride were refluxed in carbon tetrachloride for 5 hr., there was essentially no reaction as evidenced by the infrared spectrum. After evaporation of the reactants, only a small amount of tarry residue remained. When benzoylphenylacetylene was refluxed with pyridine in ether overnight there was no reaction. However, when benzoylphenylacetylene was heated at 70° in pyridine in the presence of dissolved silver chloride under conditions similar to those used in the preparation of Ia, only dark oils, but no Ia, were found.

**N-Benzoyl-2-phenylethynyl-1,2-dihydropyridine (Ia) and Benzoylphenylacetylene.**—A mixture of silver phenyl-

(23) The solubility of silver acetylides in amine solvents has been noted recently: D. Blake, G. Calvin and G. E. Coates, *Proc. Chem. Soc.*, 396 (1959); L. Barnes, Jr., *Anal. Chem.*, **31**, 405 (1959); M. Mlocque and J. A. Gautier, *Bull. soc. chim. France*, 467 (1958).

(24) J. U. Nef, *Ann.*, **308**, 264 (1899).

acetylide (7.5 g., 0.036 mole), 100 ml. of pyridine and 100 ml. of carbon tetrachloride was heated to reflux. Benzoyl chloride (5 g., 0.036 mole) in 15 ml. of pyridine was added slowly. After 0.5 hr., the mixture was cooled, filtered, poured on ice, and extracted with carbon tetrachloride. The solid was impure silver chloride (*ca.* 80%). On evaporation, the extract yielded 8.4 g. of crude Ia which was extracted with 500 ml. of hot hexane. It was crystallized from the hexane as a white solid, m.p. 123–124°, in *ca.* 70% yield. *Anal.* Calcd. for  $C_{20}H_{15}NO$ : C, 84.18; H, 5.29. Found: C, 84.42; H, 5.46.

Compound Ia did not form a picrate or quaternary salt with methyl iodide. The infrared spectrum is given in Fig. 1. The ultraviolet spectrum (see Fig. 2) has  $\lambda_{max}$  303 m $\mu$ ,  $\log \epsilon$  3.88,  $\lambda_{max}$  245 m $\mu$ ,  $\log \epsilon$  4.33, and indications that maxima at *ca.* 256 and 240 m $\mu$  are overlapped.

The hexane mother liquor from Ia was evaporated leaving 1.0 g. of an orange liquid, *ca.* 15% crude benzoylphenylacetylene. This was distilled at 121° (1 mm.) and recrystallized from hexane to m.p. 48–49° (lit.<sup>24</sup> m.p. 49–50°). The infrared spectrum of this product was identical with that of authentic benzoylphenylacetylene. With sulfuric acid, this product gave dibenzoylmethane, m.p. 79–80° (lit.<sup>24</sup> m.p. 81°). The mixture with authentic dibenzoylmethane showed no m.p. depression.

**N-Benzoyl-2-phenylethylpiperidine (V).**—Compound Ia (6.0 g., 0.02 mole) was mixed with Adams catalyst (0.6 g.) in 170 ml. of ether and subjected to *ca.* 3 atm. of hydrogen. After 3 hr. of shaking, the absorption of hydrogen leveled off at *ca.* 0.08 mole. The mixture was filtered, evaporated and the residual oil (5.9 g.) distilled at 180–190° (0.1 mm.). Three cuts of V, each with  $n_D^{20}$  1.5850, were taken; V did not form a quaternary salt with methyl iodide or a picrate. It had an infrared carbonyl band at 1626 cm.<sup>-1</sup>. *Anal.* Calcd. for  $C_{20}H_{23}NO$ : C, 81.87; H, 7.90. Found: C, 81.75; H, 7.61.

**N-Benzoyl-3-phenylethynyl-7,8-dicarboxyanhydride-2-azabicyclo(2.2.2)-7-octene (VI).**—Compound Ia (2.5 g., 0.009 mole) and maleic anhydride (3.0 g., 0.031 mole) in 100 ml. of ether were heated at reflux for 3 days. The adduct VI (2.6 g.) was ether insoluble and crystallized from acetone in white crystals, m.p. 217–219°. *Anal.* Calcd. for  $C_{24}H_{17}O_4N$ : C, 75.18; H, 4.47. Found: C, 75.33; H, 4.66.

**3-Phenylethynyl-7,8-dicarboxy-2-azabicyclo(2.2.2)-2,7-octadiene(VII).**—Compound VII was obtained from an unsuccessful attempt to prepare VI. The heating period was relatively short and only a viscous residue was obtained on evaporation of the ether. The residue was extracted with petroleum ether and acetone to yield a white solid, m.p. 168–173°. This solid was hydrolyzed with sodium hydroxide in methanol to yield another white solid which on crystallization from chloroform had m.p. 195–196°. *Anal.* Calcd. for  $C_{17}H_{15}O_4N$ : C, 68.4; H, 5.08. Found: C, 68.88; H, 5.05.

**Deuterium Exchange with Ia.**—Compound Ia was dissolved in anhydrous pyridine or triethylamine containing a few drops of deuterium oxide. After 0.5, 2 and 5 hr. at *ca.* 60°, evidence for undeuterated water in the solution was obtained by comparison of its infrared spectrum with a solution of ordinary water in these amines. Since the 2-hydrogen of Ia is associated with a weak absorption in the infrared, it was not possible to detect a C–D band. After 5 hr., the triethylamine solution was cooled and evaporated. The spectrum of the residue indicated extensive decomposition.

**2-Stilbazole (III).**—Compound Ia (5.0 g., 0.018 mole) was heated with potassium hydroxide (2.0 g.) in *ca.* 55 ml. of methanol–water (10:1) for 2 hr. on a steam-bath with ether. Three grams of impure stilbazole (III), m.p. 70–80°, recrystallized to m.p. 90.5–91° (lit.<sup>25</sup> m.p. 91°). Benzoic acid was isolated in almost quantitative yield from the aqueous layer.

The picrate of 2-stilbazole crystallized from acetone in yellow needles, m.p. 213–214° (lit.<sup>26</sup> m.p. 207°).

After an attempted oxidation of III with hydrogen peroxide in sulfuric acid, the hydrogen sulfate of III, m.p. 130–131°, from methanol, was isolated. *Anal.* Calcd. for

(25) H. Baurath, *Ber.*, **20**, 2719 (1887); **21**, 818 (1888).

(26) K. Feist, W. Awe and M. Kukilinski, *Arch. Pharm.*, **274**, 418 (1936).

$C_{13}H_{11}N \cdot H_2SO_4$ : C, 55.9; H, 4.60. Found: C, 56.08; H, 4.60. Sodium hydroxide regenerates III from this salt.

2-Stilbazole absorbed 4.6 moles of hydrogen in a low pressure hydrogenation over platinum oxide. The product, 2-(2-phenylethyl)-pyridine, was analyzed as the picrate, m.p. 126–127° (lit.<sup>27</sup> m.p. 127°).

Bromine (0.352 g., 0.00183 mole) added to 2-stilbazole (0.35 g., 0.0018 mole) in ice-cooled carbon tetrachloride gave almost quantitatively a white crystalline adduct which crystallized from methanol–acetone to m.p. 194–195°. This adduct appears to be different from the reported 2-stilbazole dibromide,<sup>21,26</sup> m.p. 166–167° or 185–186°. By analogy with the preparation of pyridine perbromide, we tentatively conclude that our adduct is the 2-stilbazole perbromide.<sup>28</sup> *Anal.* Calcd. for  $C_{13}H_{11}NBr_2$ : C, 45.77; H, 3.25. Found: C, 45.67; H, 3.39.

**Oxidation of 2-Stilbazole (III).**—This briefly describes one more method for oxidizing III.<sup>25,29,30</sup> It is also a method for oxidizing 2-picolinic acid. Compound III (5.0 g., 0.028 mole) was dissolved in acetic acid and treated with 90% hydrogen peroxide for 1 hr. on the steam-bath; 1.55 g. of benzoic acid, m.p. 118–122°, was obtained. The residue (1.7 g.) on crystallization then sublimation gave crystals, m.p. 162–164° (lit.<sup>30,31</sup> for 2-picolinic acid N-oxide, m.p. 162–163°). Titrations with standard base indicated an equivalent weight for this acid of 146, 140 (calcd. for  $C_8H_5NO_3$ , 139). From other such oxidations of III, the picrate of 2-picolinic acid was crystallized from methanol to m.p. 185–187°. *Anal.* Calcd. for  $C_{12}H_9N_4O_9$ : C, 40.8; H, 2.28. Found: C, 40.72; H, 2.84.

**2-Phenylethynylpyridine (IV).**—Compound Ia (3 g., 0.011 mole) was suspended in 10 ml. of methanol and added to a solution of bromine (1.68 g., 0.07 mole) and potassium hydroxide (1.2 g., 0.07 mole) in methanol cooled in Dry Ice. After 3 hr., the mixture was filtered. The filtrate, extracted with ether, gave a yellow oil, presumably crude N-benzoyl-2-bromo-2-phenylethynyl-1,2-dihydropyridine. This was dissolved in methanolic potassium hydroxide and warmed 10 min. on the steam-bath. The mixture was worked up to give IV as a crude oil (1.7 g., *ca.* 83%) which on distillation at 116° (0.1 mm.) (lit.<sup>21</sup> 148–150° (1 mm.)) had a medium intensity infrared absorption at 4.7  $\mu$ . When IV was treated with cold sulfuric acid–water (1:1), 2-phenacylpyridine was obtained,<sup>21</sup> m.p. 58–59° (lit.<sup>21,22,32</sup> 59°, 54°, 51°). A picrate of IV after sublimation had m.p. 150–155° dec. *Anal.* Calcd. for  $C_{19}H_{13}N_4O_7$ : C, 55.88; H, 2.96. Found: C, 56.02; H, 3.25.

**Acid Hydrolysis of Ia.**—Acid hydrolysis of Ia on the steam-bath yielded dark resins. Steam distillation of Ia (2.8 g.) with sulfuric acid–water (1:1) yielded a trace of an oil from which a dinitrophenylhydrazone, m.p. 235°, could be prepared. Mixed m.p. determinations of various fractions of this DNP with authentic benzaldehyde DNP (lit.<sup>34</sup> m.p. 235°) gave ambiguous results: in several there appeared to be no depression, in others the m.p. dropped to 210°. However, a comparison of the infrared spectra of these DNP's run as solids in KBr pellets showed conclusively that benzaldehyde was present in the steam distillate.

The Adduct of Ia and 2,4-Dinitrophenylhydrazine.—In an attempted acid hydrolysis, Ia (0.1 g.) was dissolved in absolute alcohol and warmed briefly (*ca.* 15–20 min.) with dinitrophenylhydrazine reagent. A low melting, sparingly soluble yellow solid was precipitated which on several recrystallizations from ethanol and ethyl acetate melted at 229–232°. This was a 1:1 adduct. *Anal.* Calcd. for  $C_{24}H_{21}N_5O_4$ : C, 64.58; H, 4.38. Found: C, 64.46; H, 4.49.

**1-(2-Pyridyl)-hexene.**—Silver butylacetylide was prepared from 1-hexyne (4.0 g., 0.05 mole). It was mixed with benzoyl chloride (7.0 g., 0.05 mole) in 50 ml. of carbon

(27) A. E. Tchitchibabine, *Bull. soc. chim. France*, [5] **3**, 1607 (1936).

(28) S. M. McElvain and M. A. Goese, *THIS JOURNAL*, **65**, 2227 (1943).

(29) G. Lénart, *Ber.*, **47**, 808 (1914).

(30) R. Adams and S. Miyano, *THIS JOURNAL*, **76**, 3168 (1954).

(31) H. Krause and W. Langenbeck, *Ber.*, **92**, 155 (1959); O. Dieis and R. Meyer, *Ann.*, **513**, 129 (1934).

(32) C. C. Kloppenburg and J. P. Wibault, *Rec. trav. chim.*, **65**, 393 (1946).

(33) A. Ladenburg and E. Kroener, *Ber.*, **36**, 119 (1903).

(34) T. Curtius and G. M. Dedichen, *J. prakt. Chem.*, **80**, 241 (1894).

tetrachloride and heated to reflux. Pyridine (20 g., 0.25 mole) was added slowly and the heating continued for 3 hr. Silver chloride was filtered from the mixture and the solvent was evaporated leaving 11.6 g. of a dark "oil 1." Oil 1 was treated with methanolic potassium hydroxide (as in the preparation of III) and when worked up yielded another oil (3.0 g.) which distilled at 70° (0.3 mm.) as a colorless liquid,  $n_D^{20}$  1.5305. The picrate had m.p. 123–124°. *Anal.* Calcd. for  $C_{17}H_{15}N_4O_7$ : C, 52.31; H, 4.65. Found: C, 52.29; H, 4.78.

In several of the preliminary attempts to isolate *N*-benzoyl-2-(1-hexynyl)-1,2-dihydropyridine from oil 1, the following observations were made. An ether solution of oil 1 was first washed with aqueous acid, bicarbonate solution then dried and evaporated. The residue was distilled at 135–143° (0.1–0.3 mm.) to give a clear liquid which generally darkened rapidly on standing. Benzoic acid was often isolated from the distillate or on the walls of the distillation apparatus. The distillate reacted rapidly with aniline depositing benzanilide, m.p. 162–163°. Another portion of the distillate with phenylhydrazine reagent gave the phenylhydrazone of 2-pyridinaldehyde which crystallized from ethanol and had m.p. 173–174° (lit.<sup>29</sup> m.p. 173–176°).

The presence of phenyl 1-hexynyl ketone in the distillate was also established both by the infrared spectrum and the preparation of the DNP, m.p. 145–147° (lit.<sup>3</sup> m.p. 156°). Its m.p. was not depressed when mixed with the DNP, m.p. 149–152°, prepared from authentic phenyl 1-hexynyl ketone.

*N-p*-Nitrobenzoyl-2-phenylethynyl-1,2-dihydropyridine.—To *p*-nitrobenzoyl chloride (9.3 g., 0.05 mole) and pyridine (4.8 g., 0.05 mole) in 100 ml. of refluxing carbon tetrachloride was slowly added finely ground silver phenylacetylide (10.5 g., 0.05 mole). After 12 hr., the mixture was filtered and washed three times with hot carbon tetrachloride. The residue, 10.3 g., contained 3 g. of silver phenylacetylide. The yield of crude product was 90%. It crystallized from carbon tetrachloride and had m.p. 173–174°. *Anal.* Calcd. for  $C_{20}H_{14}N_2O_3$ : C, 72.71; H, 4.27. Found: C, 72.29; H, 4.27.

*N-m*-Nitrobenzoyl-2-phenylethynyl-1,2-dihydropyridine.—To *m*-nitrobenzoyl chloride (14.1 g., 0.075 mole) and silver phenylacetylide (15.9 g., 0.075 mole) in 200 ml. of refluxing carbon tetrachloride-pyridine (23.7 g., 0.3 mole) was added. After 5 hr. the mixture was worked up to give 22.2 g. of

m.p. 135–140°, in 90% yield. Recrystallization from carbon tetrachloride gave yellow needles, m.p. 144–145°. *Anal.* Calcd. for  $C_{20}H_{14}N_2O_3$ : C, 72.71; H, 4.27. Found: C, 72.75; H, 4.36.

**Attempt to Prepare *N-p*-Anisoyl-2-phenylethynyl-1,2-dihydropyridine.**—When *p*-anisoyl chloride was treated with silver phenylacetylide and pyridine in carbon tetrachloride in the usual manner, the dihydropyridine could not be isolated in pure form. Basic hydrolysis, however, led to stilbazole, m.p. 88–90°, in 50% yield (based on *p*-anisoyl chloride); *p*-methoxybenzoic acid, m.p. 176° (lit.<sup>35</sup> m.p. 180–182°) was also isolated.

***N*-Benzoyl-2-phenylethynyl-dihydroquinoline.**—Silver phenylacetylide (4.2 g., 0.02 mole), benzoyl chloride (3.2 g., 0.022 mole) and 20 ml. of quinoline in 50 ml. of carbon tetrachloride were refluxed overnight and worked up. The oily residue was crystallized from methanol-acetone to give white crystals, m.p. 133–134°, in ca. 40% yield. *Anal.* Calcd. for  $C_{24}H_{17}ON$ : C, 85.93; H, 5.11. Found: C, 85.90; H, 5.22.

**2-Phenacylpyridine.**—In an attempt to prepare the analog of I from 2-methylpyridine, the phenacylpyridine was produced. Silver phenylacetylide (7 g.), benzoyl chloride (4.5 g.) and 2-methylpyridine (3 g.) were refluxed in carbon tetrachloride in the usual way. Silver chloride (4.5 g.) as well as a dark oil (3.5 g.) contaminated with benzoyl chloride were isolated. On treatment with alcoholic base, the oil gave another liquid as well as benzoic acid. The picrate of 2-phenacylpyridine was prepared from this liquid and had m.p. 176–178° (lit.<sup>33</sup> m.p. 176–177°).

***p*-Chlorobenzoic Anhydride.**—Attempts to prepare the *p*-chlorobenzoic analog of Ia in the usual way were unsuccessful. Instead, *p*-chlorobenzoic anhydride was obtained, m.p. 195–196°, from acetone (lit.<sup>36</sup> m.p. 193–194°). Prior treatment of the *p*-chlorobenzoyl chloride with thionyl chloride and distillation did not lead to the desired product. Apparently, traces of water or *p*-chlorobenzoic acid remained in the starting material and formed the anhydride, or the desired reaction was very slow and the anhydride was formed during the working up of the products.

(35) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, **97**, 1732 (1910).

(36) R. Adams, W. V. Wirth and H. E. French, *THIS JOURNAL*, **40**, 424 (1918).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y., AND THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY, NEW BRUNSWICK, N. J.]

## The Formation of Cycl[3.2.2]azine Derivatives *via* the Reaction of Pyrrocoline with Dimethyl Acetylenedicarboxylate

BY ANDREW GALBRAITH,<sup>1a,2</sup> THEODORE SMALL,<sup>1a,3</sup> RODERICK A. BARNES<sup>1b</sup> AND V. BOEKELHEIDE<sup>1a,4</sup>

RECEIVED JULY 13, 1960

The reaction of pyrrocoline with dimethyl acetylenedicarboxylate in the presence of a dehydrogenation catalyst gives 1,2-dicarbomethoxycycl[3.2.2]azine (I) plus some 1,2-dicarbomethoxy-3,4-dihydrocyclo[3.2.2]azine (XVIII). The evidence for these structures as well as a theoretical consideration of the reaction mechanism is presented.

In their extensive studies on the reaction of heterocyclic amines with dimethyl acetylenedicarboxylate, Diels and his collaborators discovered a series of interesting and unusual products.<sup>5</sup> In the case of the six-membered heterocycles, pyridine and its various derivatives, the reaction involves attack on the nitrogen atom. Originally these products were formulated as zwitterionic compounds, but

the recent work of Acheson and Taylor clearly demonstrates that they are quinolizine derivatives.<sup>6a,b</sup> However, with five-membered heterocycles such as pyrrole, the normal course is one of substitution to introduce an  $\alpha,\beta$ -dicarbomethoxyvinyl residue.<sup>7</sup> It was of interest, therefore, to study the case of pyrrocoline in which the nitrogen atom is common to both a six- and a five-membered ring, since it might be anticipated that an initial substitution reaction would, in this case, be followed by ring

(1) (a) University of Rochester; (b) Rutgers University.

(2) Alfred P. Sloan Foundation Fellow, 1958–1959.

(3) Monsanto Predoctoral Fellow, 1958–1959.

(4) To whom inquiries should be addressed. University of Oregon, Eugene, Ore.

(5) See O. Diels and H. Schrum, *Ann.*, **530**, 68 (1937), for leading references.

(6) (a) R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1691 (1960); (b) for an earlier study by R. B. Woodward and E. C. Kornfeld, see E. C. Kornfeld, Ph.D. Thesis, Harvard University, 1945.

(7) O. Diels, K. Alder, H. Winkler and E. Petersen, *Ann.*, **498**, 1 (1932).