[Experimental Biology and Medicine Institute, National Institutes of Health]

SYNTHESIS OF A SERIES OF COMPOUNDS CONTAINING A QUATERNARY CARBON ATOM[1]

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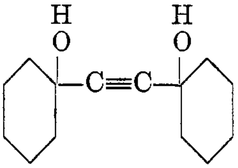
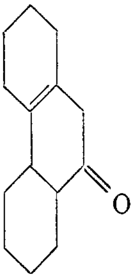
Recently, we became interested in a series of compounds which contain a quaternary carbon atom and a tertiary amine group, in order to study their analgesic activities. In the course of the investigation, it soon became evident that we had the key to a controversial problem. Pinkney, Nesty, Wiley, and Marvel (1) studied the dehydration and cyclization of 1,1'-ethynylene-*bis*-cyclohexanol (I), and they assumed their product to be Δ^{11}-dodecahydrophenanthrone-9 (II).



I



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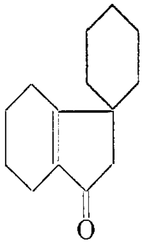
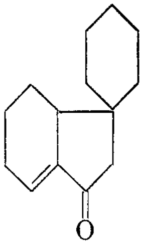


III



IV

Linstead and Walpole (2), in a very meticulous manner, isolated two solid ketones (m.p. 38–39° and m.p. 93–94°) from the product of the cyclodehydration of 1,1'-ethynylene-*bis*-cyclohexanol (I). Both of these substances were α,β-unsaturated ketones as indicated by ultraviolet absorption spectra. In addition, Woodward, still uncertain of the spirane or phenanthrene structure, showed that the ketone melting at 39° contained an exocyclic carbon-carbon double bond, and the ketone melting at 94° contained α,β-unsaturation within the same ring (3). These ketones are designated as III (m.p. 94°) and IV (m.p. 39°).

Linstead and Doering (4) in their preparation of all of the isomeric perhydrodiphenic acids proved that the dibasic acid obtained from Marvel's cyclized ketones, III and IV, by reduction of the double bond and subsequent oxidation (2) was not the same as any of their diphenic acids. Levitz, Perlman, and Bogert (5) synthesized spiro[cyclohexane-1,1'-indane] in order to show that the cyclodehydration of 1-β-phenylethylcyclohexanol-1 could yield a spirane compound as well as a phenanthrene. In the course of their work, they synthesized spiro-[cyclohexane-1,1'-indanone-3'] (VI). However, in spite of the accumulation of evidence indicating that Marvel had a spirane instead of a phenanthrene type

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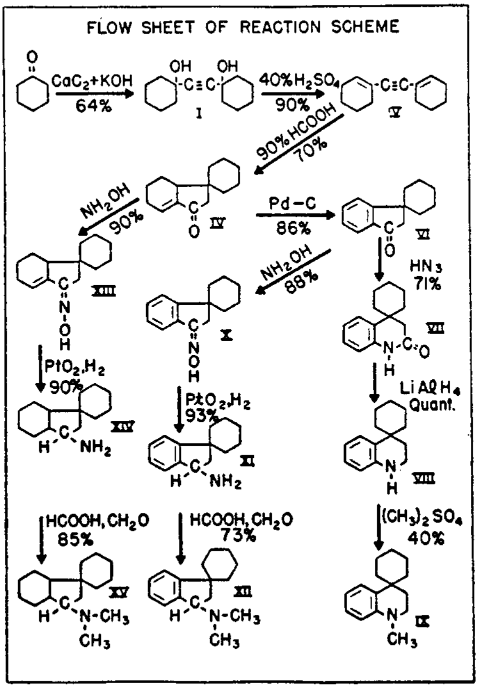
compound, no one had shown conclusively that his ketonic product was a spiro[cyclohexane-1,1′-tetrahydroindanone-3′] (III or IV).

With slight variations in procedure, Marvel's work was repeated and a ketonic product boiling at 130–132° (2 mm.) was isolated. Preparation of a 2,4-dinitrophenylhydrazone of the ketone produced a red substance melting at 224–225°. The oxime was prepared and yielded 90% of brilliant massive polyhedra melting at 183.5–184°. These compounds check very closely the derivatives made from the ketone melting at 39° (1, 2), and we shall therefore use structure IV in this paper to indicate the ketonic product of cyclodehydration.

CHART I



When this ketone was dehydrogenated over a palladium charcoal catalyst, spiro[cyclohexane-1,1′-indanone-3′] (VI) was produced in excellent yields. Since this compound is the same that Bogert and coworkers (5) synthesized by an alternate method, we conclude that Marvel was dealing with a spirane of proved carbon skeleton and not a phenanthrene, that the position of the carbonyl group is established, and that Woodward's formulations involving the relationship of the double bond and the carbonyl group are now valid in entirety.

The synthesis of a series of compounds containing a quaternary carbon atom and a tertiary, methylated amine proceeds as indicated in Chart I.

The Schmidt reaction on spiro[cyclohexane-1,1′-indanone-3′] (VI) could possibly lead to a dihydrocarbostyril compound (VII) or to a dihydroisocarbostyril compound, although from the experimental evidence on this reaction with alkyl aryl ketones (6), one would expect to find the dihydrocarbostyril in the greater yield. Spiro[cyclohexane-1,1′-indanone-3′] (VI) when subjected to the Schmidt reaction with 90% sulfuric acid and powdered sodium azide produced the crystalline spiro[cyclohexane-1,4′-dihydrocarbostyril] (VII) in 71% yields. This compound was then reduced quantitatively with lithium aluminum hydride to spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] (VIII).

In order to prove that the amine was a tetrahydroquinoline and not a tetrahydroisoquinoline a comparison of the ultraviolet absorption spectra (Figure 1) of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and the synthetic amine, spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] (VIII) was made. These curves show conclusively that the Schmidt reaction produced the normal compound in which the amino group was injected adjacent to the aryl group in an aryl alkyl ketone and which subsequently was reduced to a tetrahydroquinoline type compound (VIII).

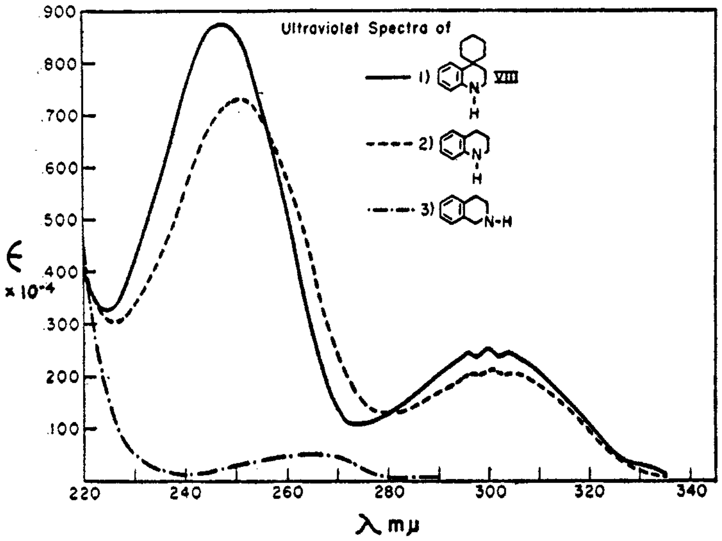


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA of 1,2,3,4-Tetrahydroquinoline, 1,2,3,4-Tetrahydroisoquinoline, and Spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline].

Chemically, the amine (VIII) reacts with formaldehyde and formic acid to produce a high molecular weight substance, which could not be characterized readily. A sample of 1,2,3,4-tetrahydroquinoline also gave a polymeric material when subjected to formaldehyde-formic acid treatment, but with 1,2,3,4-tetrahydroisoquinoline normal N-methylation resulted, and a good yield of isokairoline was obtained.

Since N-methylation of spiro[cyclohexane 1,4′-1′,2′,3′,4′-tetrahydroquinoline] using formaldehyde and formic acid was not successful, resort was had to dimethyl sulfate; the tertiary amine (IX) was obtained in 40% yield.

Oximination of spiro[cyclohexane 1,1′-indanone-3′] (VI) in pyridine and absolute alcohol gave (X) in excellent yields. Hydrogenation of this oxime at room temperature and atmospheric pressure with Adams' catalyst produced spiro[cyclohexane-1,1′-3′-aminoindane] (XI), which upon subsequent methylation with formaldehyde and formic acid produced spiro[cyclohexane-1,1′-3′-dimethylaminoindane] (XII).

Reduction of the oxime (XIII) with Adams' catalyst in glacial acetic acid at room temperature and atmospheric pressure produced spiro[cyclohexane-1,1′-3′-aminohexahydroindane] (XIV). This amine was then methylated to give good yields of spiro[cyclohexane-1,1′-3′-dimethylaminohexahydroindane] (XV).

Analgesic testing on this series of compounds is being done by Dr. Nathan B. Eddy of this Institute. Preliminary results indicate that all the amine compounds, VIII, IX, XI, XII, XIV, and XV, exhibit analgesic activity. A more detailed report of these activities will be reported elsewhere after completion of the tests.

Acknowledgement. The author wishes to express his thanks to Drs. Lyndon F. Small, Erich Mosettig, and G. Forrest Woods for their suggestions during the course of this research. Microanalyses were performed by William Alford, Margaret Ledyard, and Evelyn Peake of this Institute.

EXPERIMENTAL

All melting points and boiling points given are uncorrected.

1,1′-Ethynylene-bis-cyclohexanol (I). This preparation is a modification of the ethynylation procedure of Kazarin (7). Into a mixture of 382 g. of calcium carbide, 240 g. of finely powdered technical potassium hydroxide, and 2500 ml. of anhydrous benzene cooled to 0–5°, 425 g. of cyclohexanone was added dropwise with vigorous stirring over a period of two hours; additional stirring was continued for four hours, and then the mixture left for 48 hours at room temperature. The congealed mass was decomposed at 0–5° with two liters of 50% hydrochloric acid and the filtered, crude, grey solid air-dried overnight. Recrystallization from boiling carbon tetrachloride yielded 295 g. or 64% of white, crystalline 1,1′-ethynylene-*bis*-cyclohexanol. An analytical sample, prepared by recrystallization from acetone and sublimation at 120° (1 mm.), melted at 109–110°; lit. m.p. 109–110°.

Anal. Calc'd for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0.

Found: C, 75.6; H, 10.4.

Spiro[cyclohexane-1,1′-$\Delta^{9'}$-tetrahydroindanone-3′] (IV). The procedure for the dehydration and cyclization of the acetylenic glycol (I) is essentially that of Marvel and coworkers (1). Sixty-four grams (0.288 mole) of 1,1′-ethynylene-*bis*-cyclohexanol was refluxed for 2½ hours with 300 ml. of 40% sulfuric acid. The organic layer was separated from the cooled mixture, and the aqueous layer extracted with ether. The combined organic layer and ether extracts were washed until neutral, and the solvent removed under reduced pressure. The crude dieneyne V was then refluxed for 2½ hours with 450 ml. of 90% formic acid. The cooled mixture was extracted with ether, the ether extract washed until neutral, and then dried over magnesium sulfate. The solution was distilled under reduced pressure: spiro-[cyclohexane-1,1′-$\Delta^{9'}$-tetrahydroindanone-3′] (38 g., 64%) b.p. 130–132° (2 mm.), n_D^{20} 1.5326; lit. b.p. 130–132° (2 mm.), n_D^{20} 1.5315.

The red *2,4-dinitrophenylhydrazone* prepared in the usual manner melted at 224–224.5° after recrystallization from ethyl acetate; lit. m.p. 227–228°.

Anal. Calc'd for $C_{20}H_{24}N_4O_4$: C, 62.3; H, 6.3.

Found: C, 62.4; H, 6.5.

Spiro[cyclohexane-1,1′-$\Delta^{9'}$-tetrahydroindanone-3′] (IV) (6.2 g.) was added to a mixture of hydroxylamine hydrochloride (7.0 g.), pyridine (13 ml.), and absolute alcohol (33 ml.), and the solution refluxed for 3½ hours. After removal of the solvent under reduced pressure, the resulting crystalline mass was recrystallized from an alcohol-water mixture to yield the *oxime* of spiro[cyclohexane-1,1'-$\Delta^{9'}$-tetrahydroindanone-3'] (XIII) (6.0 g. or 90%) which melted at 180–183°: the analytical sample was recrystallized very slowly from 70% petroleum ether (30–60°)-alcohol solutions to produce brilliant, massive polyhedra melting at 183.5–184.0°; lit. m.p. 183–184°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.7; H, 9.7.
Found: C, 76.7; H, 9.7.

Spiro[cyclohexane - 1,1' - indanone - 3'] (VI). Spiro[cyclohexane - 1,1' - $\Delta^{9'}$ - tetrahydro-indanone-3'] (IV, 25 g.) was added to 10 g. of a 5% Pd-C catalyst and 20 ml. of *p*-cymene. *p*-Cymene was distilled off until the temperature of the mixture reached 285–295°, then the distillation was discontinued, and the mixture refluxed for an additional four hours at this temperature range. The cooled mixture was filtered from the catalyst and distilled: spiro[cyclohexane-1,1'-indanone-3'] (VI) (21.1 g., 86%) boiled at 139–145° (4 mm.), n_D^{20} 1.5574. When several drops of the ketone were added to petroleum ether (30–60°) and the mixture scratched and chilled in a Dry Ice-bath, a copious white precipitate formed which was used to seed the rest of the ketone. An analytical sample, prepared by sublimation at 60° (0.5 mm.), melted at 53–54°; lit. m.p. 58–59°.

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.1.
Found: C, 84.0; H, 8.5.

Spiro[cyclohexane-1,1'-indanone-3'] (15 g.) was added to a mixture of hydroxylamine hydrochloride (17.5 g.), pyridine (32 ml.), and anhydrous alcohol (81 ml.), and the solution refluxed for 3½ hours. Removal of the solvent under reduced pressure, and recrystallization of the crystalline mass from alcohol-water mixture afforded the *oxime* of spiro-[cyclohexane-1,1'-indanone-3'] (X) (m.p. 127–129°, 14.1 g., 88%), which after further recrystallization from absolute alcohol melted at 138–139°; lit. m.p. 137–138°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0.
Found: C, 77.9; H, 7.9.

Semicarbazone. The ketone (1 ml.) was dissolved in alcohol (10 ml.) and water added until the solution became turbid, then a few additional drops of alcohol were added. To this mixture was added semicarbazide hydrochloride (1.0 g.) and sodium acetate (1.5 g.) and the mixture was shaken vigorously for 30 minutes and then put in boiling water and allowed to cool overnight. The white semicarbazone, recrystallized from an alcohol-water mixture, melted at 213–214°; lit. m.p. 211.5–212.5°.

Anal. Calc'd for $C_{15}H_{19}N_3O$: C, 70.0; H, 7.4.
Found: C, 70.0; H, 7.6.

Spiro[cyclohexane-1,4'-dihydrocarbostyril] (VII). Spiro[cyclohexane-1,1'-indanone-3'] (13.8 g.) was dissolved in benzene (125 ml.); water (3.3 ml.), and concentrated sulfuric acid (30.4 ml.), enough to make a 90% sulfuric acid solution, was then added and the mixture heated to 55°. Finely powdered sodium azide (6.8 g.) was added portion-wise with mechanical stirring over a period of 20 minutes. The mixture, kept at this temperature and stirred continuously for 30 minutes after the evolution of nitrogen had ceased, was cooled and the benzene layer decanted from the sulfuric acid layer. Ice was added, with efficient cooling and mechanical stirring, to the sulfuric acid layer. Continual stirring for one hour and the addition of small portions of ether caused the oily layer to crystallize. Yellow, solid spiro[cyclohexane-1,4'-dihydrocarbostyril] (10.5 g., 71%) so formed is pure enough for use in subsequent reactions. Recrystallization from alcohol-water mixture produced a white, analytical sample melting at 185–185.5°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0.
Found: C, 78.1; H, 8.2.

Spiro[cyclohexane-1,4'-1',2',3',4'-tetrahydroquinoline] (VIII). To 100 ml. of a cooled 1.2 molar (100% excess) solution of lithium aluminum hydride in ether, 26.6 g. of VII in 200 ml. of dry benzene was added dropwise over one hour; the reaction was vigorous. The ether was then removed by distillation and the mixture refluxed for 24 hours to produce a voluminous white precipitate. This complex was decomposed in the cold with just enough water to precipitate all of the aluminum hydroxide. Then the benzene layer was decanted, and the gelatinous residue extracted with ether. The amine was isolated by acid-base extraction and the viscous, yellow oil distilled under nitrogen: b.p. 156–157° (1.5 mm.), 23.7 g., or 96%. It crystallized from petroleum-ether (30–60°) in a Dry Ice-bath and sublimed readily under reduced pressure to yield white crystals melting at 40–40.5°.

Anal. Calc'd for $C_{14}H_{19}N$: C, 83.5; H, 9.5.

Found: C, 83.5; H, 9.7.

The *N-acetyl* derivative formed by refluxing the amine (VIII) in acetic anhydride, recrystallized from water and sublimed at reduced pressure, melted at 99–100°.

Anal. Calc'd for $C_{16}H_{21}NO$: C, 79.0; H, 8.7.

Found: C, 79.0; H, 8.7.

The *N-benzoyl* derivative, made by treating the amine (VIII) (1 g.) with benzoyl chloride (1 g.) and 20% sodium hydroxide (5 ml.), was recrystallized from absolute alcohol and melted at 131–132°.

Anal. Calc'd for $C_{21}H_{23}NO$: C, 82.6; H, 7.6.

Found: C, 82.9; H, 7.7.

Spiro[cyclohexane-1,4'-N-methyl-1',2',3',4'-tetrahydroquinoline] (IX). A suspension of 2.7 g. of the amine VIII in 10 ml. of water was refluxed for four hours with 1.73 g. of dimethyl sulfate, and then allowed to stand for 48 hours at room temperature. Ammonium hydroxide was added and the basic solution extracted with ether. The amine (2.5 g.) was isolated in the usual manner. This oil was reacted with benzoyl chloride and dilute sodium hydroxide and the unreacted oil extracted with ether. Spiro[cyclohexane-1,4'-N-methyl-1',2',3',4'-tetrahydroquinoline] (1.25 g., 43%) isolated in the usual manner was distilled under nitrogen: b.p. 134–135° (1 mm.), n_D^{30} 1.5778.

Anal. Calc'd for $C_{15}H_{21}N$: C, 83.7; H, 9.8.

Found: C, 83.7; H, 9.8.

The *picrate* was formed in the usual manner and after several recrystallizations from absolute alcohol melted at 170–172°.

Anal. Calc'd for $C_{21}H_{24}N_4O_7$: C, 56.8; H, 5.4.

Found: C, 56.6; H, 5.5.

Spiro[cyclohexane-1,1'-3'-aminoindane] (XI). The oxime of spiro[cyclohexane-1,1'-indanone-3'] (X) (17.5 g.) was hydrogenated at room temperature and atmospheric pressure in a glacial acetic acid solution (100 ml.) using Adams' catalyst (1.0 g.). The theoretical amount of hydrogen was absorbed in four hours. After the catalyst was removed by filtration, the solvent was distilled off under reduced pressure to give the acetylated amine, which was hydrolyzed by refluxing in 20% sodium hydroxide (100 ml.) for three hours. The amine was isolated from the cooled solution by acid-base extraction. The dried ether solution was distilled under nitrogen to yield spiro[cyclohexane-1,1'-3'-aminoindane] (10.5 g., 64%): b.p. 115–117° (1 mm.), n_D^{30} 1.5512. The free amine is very hygroscopic, which is reflected in the analytical value.

Anal. Calc'd for $C_{14}H_{19}N$: C, 83.5; H, 9.5.

Found: C, 82.9; H, 10.1.

The *benzoyl* derivative was made in the usual manner and after recrystallization from alcohol melted at 164–165°.

Anal. Calc'd for $C_{21}H_{23}NO$: C, 82.6; H, 7.6.

Found: C, 82.3; H, 7.4.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XI, melted at 245–246° after recrystallization from an absolute alcohol-ether mixture.

Anal. Calc'd for $C_{14}H_{20}ClN$: C, 70.7; H, 8.5; Cl, 15.2.

Found: C, 70.3; H, 8.7; Cl, 15.3.

Spiro[cyclohexane-1,1'-3'-dimethylaminoindane] (XII). To a cooled solution of 3 g. of the amine (XI) and 3.5 g. of 90% formic acid, 3.5 g. of a 36% aqueous solution of formaldehyde was added (8). Upon warming this mixture to room temperature a vigorous evolution of carbon dioxide ensued and lasted for one hour, after which the mixture was refluxed on a steam-bath overnight. Isolation of the amine was accomplished in the usual manner. This product was then treated with 30 ml. of 20% sodium hydroxide and 8 ml. of acetic anhydride. The tertiary amine (2.5 g. or 73%), isolated from this mixture in the usual manner, boiled at 123–124° (0.8 mm.), n_D^{35} 1.5400.

Anal. Calc'd for $C_{16}H_{23}N$: C, 83.8; H, 10.1.
Found: C, 83.4; H, 10.3.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XII, melted at 237–238° after recrystallization from absolute alcohol-ether mixtures.

Anal. Calc'd for $C_{16}H_{24}ClN$: C, 72.3; H, 9.1.
Found: C, 72.2; H, 9.2.

The *picrate*, formed in the usual manner and recrystallized from absolute alcohol, melted at 190–191°.

Anal. Calc'd for $C_{22}H_{26}N_4O_7$: C, 57.6; H, 5.7.
Found: C, 57.8; H, 5.9.

The *methiodide*, formed in the usual manner and recrystallized from absolute alcohol, melted at 187–189°.

Anal. Calc'd for $C_{17}H_{26}IN$: C, 55.0; H, 7.1.
Found: C, 54.7; H, 7.1.

Spiro[cyclohexane-1,1'-3'aminohexahydroindane] (XIV). This compound was prepared in 90% yields in the same manner as the corresponding aromatic amine (XI): b.p. 119–121° (1.8 mm.), n_D^{20} 1.5128.

The *N-benzoyl* derivative was made in the usual manner and after recrystallization from an alcohol-water mixture melted at 184–185°.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 81.0; H, 9.4.
Found: C, 81.0; H, 9.4.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XIV, melted at 290–295° after recrystallization from alcohol-ether mixtures.

Anal. Calc'd for $C_{24}H_{26}ClN$: C, 69.0; H, 10.8.
Found: C, 68.9; H, 10.6.

Spiro[cyclohexane-1,1'-3'-dimethylaminohexahydroindane] (XV). The tertiary amine was prepared and isolated in the same manner as the corresponding aromatic amine XII, in 85% yield: b.p. 127–128° (1.8 mm.), n_D^{28} 1.5053.

Anal. Calc'd for $C_{16}H_{29}N$: C, 81.6; H, 12.4.
Found: C, 81.2; H, 12.4.

The *picrate* was formed in the usual manner, and after recrystallization from absolute alcohol melted at 168–170°.

Anal. Calc'd for $C_{22}H_{32}N_4O_7$: C, 56.9; H, 6.9.
Found: C, 57.0; H, 7.2.

The *methiodide*, prepared in the usual manner, was recrystallized from absolute alcohol and melted at 190–192°.

Anal. Calc'd for $C_{17}H_{32}IN$: C, 54.1; H, 8.6.
Found: C, 53.9; H, 8.6.

N-Methylation of 1,2,3,4-tetrahydroisoquinoline. 1,2,3,4-Tetrahydroisoquinoline was purified by recrystallization of its hydrochloride and subsequent regeneration and distillation: b.p. 82–82.5° (3 mm.) n_D^{23} 1.5790. The formic acid-formaldehyde methylation procedure was the same as that used in previous parts of this paper. Isokairoline [b.p. 81–86° (2 mm.)] was obtained in 80% yields and produced a *methiodide*, which after recrystallization from absolute alcohol, melted at 188–189° (Literature, m.p. 188–189°).

Ultraviolet absorption spectra. All measurements were made on a Beckman spectrophotometer on absolute alcohol solutions. Commercial 1,2,3,4-tetrahydroquinoline was redistilled and the fraction b.p. 68.0–68.5° (1.5 mm.), n_D^{25} 1.5910 used in this analysis. Cell length was 1.007 cm. and concentration 8.2×10^{-5} molar. 1,2,3,4-Tetrahydroisoquinoline was purified as indicated previously. Cell length was 0.999 cm. and concentration 8.92×10^{-5} molar. The spectrum of spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] was taken on the analytical sample; 3.2×10^{-5} molar concentration with a 1.006-cm. cell being used.

SUMMARY

1. Strong evidence is presented which indicates that the cyclodehydration of 1,1′-ethynylene-*bis*-cyclohexanol produces a mixture of spirano-ketones and not a phenanthrone type compound.

2. A new series of compounds containing a quaternary carbon atom and a tertiary amine group has been synthesized.

3. These compounds were tested and each one showed analgesic activity.

Bethesda 14, Md.

REFERENCES

(1) Pinkney, Nesty, Wiley, and Marvel, *J. Am. Chem. Soc.*, **58**, 972 (1936).
(2) Linstead and Walpole, *J. Chem. Soc.*, 842, 850 (1939).
(3) Woodward, *J. Am. Chem. Soc.*, **64**, 76 (1942).
(4) Linstead and Doering, *J. Am. Chem. Soc.*, **64**, 1991 (1942).
(5) Levitz, Perlman, and Bogert, *J. Org. Chem.*, **6**, 105 (1941).
(6) Wolff, *Org. Reactions*, **3**, 315 (1947).
(7) Kazarin, *J. Gen. Chem.* (*U.S.S.R.*), **4**, 1347 (1934) [*Chem. Abstr.*, **29**, 3978 (1935)].
(8) Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).