

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Aromatic Cyclodehydration. XLVI.<sup>1</sup> Synthesis of Tetrahydropalmatine and Its Analogs<sup>2</sup>

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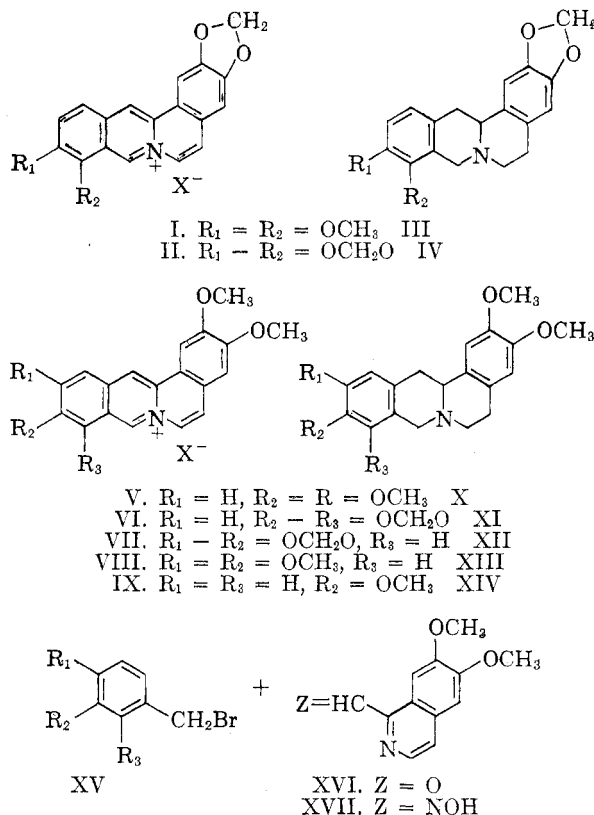
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Tetrahydropalmatine (X) and a number of protoberberine alkaloids (XI–XIV) have been synthesized from 6,7-dimethoxyisoquinoline-1-carboxaldehyde (XVI) and its oxime (XVII) by following the general procedure described earlier. Tetrahydrocoptisine or stylophine (IV) has also been synthesized from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde.

It has been shown<sup>3</sup> that tetrahydroberberine (III) could be synthesized from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde or its oxime, using the methods of quaternization and cyclodehydration developed earlier.<sup>4</sup> The present communication describes the synthesis of 6,7-dimethoxyisoquinoline-1-aldehyde (XVI) and its use in the synthesis of tetrahydropalmatine (X), and some related compounds.

By following the same procedure, tetrahydrocoptisine (or stylophine IV) has been prepared from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde.<sup>3</sup>

It was found that 1-methyl-6,7-dimethoxyisoquinoline, conveniently prepared by the Bischler-Napieralski cyclization of homoveratrylacetylacetamide, followed by dehydrogenation,<sup>5</sup> could be oxidized to the corresponding aldehyde in 35% yield by the action of selenium dioxide. When this new aldehyde was quaternized in the usual way with 2,3-dimethoxybenzyl bromide (XV,  $R_1 = H$ ,  $R_2 = R_3 = OCH_3$ ) in the presence of acetonitrile<sup>3</sup> and the crude salt with cyclized by heating it with concentrated hydrochloric acid, the over-all yield of the new dehydropalmatine bromide (V,  $X = Br$ ), was only 30%. The yield was raised to 80% when the oxime (XVII) of the 6,7-dimethoxyisoquinoline-1-carboxaldehyde (XVI) was used, and the quaternization effected in presence of dimethylformamide. It has also been found that the oxime method is superior in the case of synthesis of other analogs. The ultraviolet and visible spectra of the dehydropalmatine bromide (V,  $X = Br$ ) thus prepared, resembled those of benz-[a]acridinium salts previously prepared.<sup>4</sup> Reduction of the new salt (V,  $X = Br$ ) in presence of Adams' catalyst produced ( $\pm$ )-tetrahydropalmatine as the hydrobromide, and the free base (X) was found to be identical with an authentic sample.<sup>6,7,8</sup> Other analogs tetrahydropalmatine were obtained by starting with the appropriate alkoxybenzyl halides. The oxime (XVII) was quaternized with 2,3-methylenedioxybenzyl bromide<sup>4</sup> (XV,  $R_1 = H$ ,  $R_2 = R_3 = OCH_2O$ ) and the crude salt was cyclized with hydrochloric acid, affording the expected dehydroepiberberinium chloride (VI,  $X = Cl$ ; 65% yield). Catalytic hydrogenation of the new salt (VI,  $X = Cl$ ) afforded the tetrahydroepiberberine<sup>9,10</sup> (XI).



(1) For the preceding communication of this series, see C. K. Bradsher and T. W. G. Solomons, *J. Org. Chem.*, **25**, 191 (1960).

(2) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, and was presented before the International Symposium on the Chemistry of Natural Products, Melbourne, Australia, August 15–25, 1960. A preliminary communication appeared in *Nature*, **184**, 1943 (1959).

(3) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).

(4) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

(5) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(6) E. Späth and H. Quietensky, *Ber.*, **58**, 2267 (1925); E. Späth and E. Mosettig, *Ber.*, **59**, 1496 (1926); E. Späth and E. Kruba, *Monatsh.*, **50**, 341 (1928).

(7) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, Jr., *J. Chem. Soc.*, 548 (1927).

(8) T. R. Govindachari, S. Radjuraj, M. Subramanian, and N. Viswanthan, *J. Chem. Soc.*, 2943 (1957).

sinactine) in 50% yield. Buck and Perkin, Jr.,<sup>11</sup> following a procedure described by Pictet and Gams,<sup>12</sup> synthesized a new compound, which they named tetrahydropseudoepiberberine. This alkaloid can be prepared conveniently by cyclization of the quaternary salt obtained from the oxime (XVII) and 3,4-methylenedioxybenzyl bromide,<sup>1,13</sup> followed by catalytic reduction of the resulting dehydropseudoepiberberinium chloride (VII. X = Cl).

In the same way, when veratryl bromide was quaternized with the oxime (XVII), and cyclized as above, the dehydronorcoralydine chloride (VIII. X = Cl) was obtained in 75% yield. On catalytic reduction of the salt (VIII. X = Cl), the expected ( $\pm$ )-norcoralydine (XIII) hydrochloride<sup>14</sup> was obtained in 60% yield.

With *m*-methoxybenzyl bromide and the oxime (XVII), the 2,3,10-trimethoxybenz[a]acridizinium chloride (IX. X = Cl) was prepared as above in good yield. The catalytic reduction of the salt (IX. X = Cl) yielded the expected new alkaloid, 2,3,10-trimethoxydibenzo[a,g]quinolizidine (XIV).

When the oxime of 6,7-methylenedioxyisoquinoline-1-carboxaldehyde<sup>3</sup> was quaternized with 2,3-methylenedioxybenzyl bromide,<sup>4</sup> the crude salt was found to cyclize easily, producing the expected dehydrocoptisine chloride (II. X = Cl) in 85% yield. The catalytic reduction of the salt afforded tetrahydrocoptisine (( $\pm$ )-stylopine,<sup>9,15,16</sup> IV).

#### EXPERIMENTAL<sup>17</sup>

**1-Methyl-6,7-dimethoxyisoquinoline.** The homoveratrylamine, required for this purpose, was best prepared from 3,4-dimethoxynitrostyrene<sup>18</sup> by reduction with lithium-aluminum hydride in tetrahydrofuran, an improvement over the Soxhlet extraction method using ether.<sup>19,20</sup> The

method is essentially that described earlier<sup>21,22</sup> and the yield of the amine obtained was up to 85%. For most of our experiments we used homoveratrylamine generously donated by the Lilly Research Laboratories (Eli Lilly & Co., Indianapolis, Ind.).

1-Methyl-3,4-dihydro-6,7-dimethoxyisoquinoline, prepared by cyclization of the crude homoveratrylacetamide, was dehydrogenated by heating 20.5 g. for 2 hr. with 6 g. of 10% palladium-on-charcoal catalyst at 175°, and crystallizing the product from benzene-petroleum ether (b.p. 30–60°) as colorless needles, m.p. 112° (lit.,<sup>5</sup> m.p. 111–112°); yield 15 g. (74%). Purification was effected by passing it through a column of alumina, eluting it with benzene.

**6,7-Dimethoxyisoquinoline-1-carboxaldehyde.**<sup>23</sup> To a clear hot and stirred solution of selenium dioxide (3.5 g.) in dioxane (50 ml.) and water (3 ml.), was added dropwise a solution of 1-methyl-6,7-dimethoxyisoquinoline (5 g.) in purified dioxane (50 ml.) in the course of 30 min. Within a short time, a red precipitate started forming and the whole mixture was heated on the steam bath with continuous agitation for 2 hr., after which the solution was filtered hot from the precipitated selenium. The bulk of the dioxane was removed by distilling the filtrate, under diminished pressure. The residual material was diluted with water, made alkaline with sodium hydroxide solution, and exhaustively extracted with ether. The dark colored ethereal solution was dried (sodium sulfate) and decolorized with Norit. The almost colorless solution was filtered and freed from ether and dioxane. The residue was crystallized from ethanol. The aldehyde was obtained as colorless plates, m.p. 176°; yield 1.8 g. (35%).

*Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>: C, 66.40; H, 5.07; N, 6.45. Found: C, 66.18; H, 5.28; N, 6.85.

The oxime (XVII) of the aldehyde (XVI), prepared in the usual way, crystallized from ethanol as colorless plates, m.p. 247–248°.

*Anal.*<sup>24</sup> Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: N, 12.06. Found: N, 12.02.

**2,3,9,10-Tetramethoxybenz[a]acridizinium bromide (dehydropalmatine bromide, V, X = Br).**<sup>25</sup> (a) *By the aldehyde method.* One gram of aldehyde (XVI) was refluxed for 2 hr. with 1.2 g. of 2,3-dimethoxybenzyl bromide<sup>25</sup> in 15 ml. of acetonitrile, under a nitrogen atmosphere. The solvent was removed under vacuum and the red semisolid residue was washed several times with ether. Concentrated hydrochloric acid (20 ml.) was then added to the solid which slowly went into solution. The solution was heated on the steam bath for about 1 hr. The solvent was removed under diminished pressure, and the residue was crystallized from ethanol, producing orange needles, m.p. 250° dec. (in sealed tube); yield 0.61 g. (30%). The yield was not improved by changing the solvent or the refluxing time.

(b) *By the oxime method.* The oxime (XVII, 1 g.) was dissolved in 20 ml. of dimethylformamide by heating on a steam bath and 1 g. of 2,3-dimethoxybenzylbromide was added to the hot solution. The whole mixture was kept at 50° for about 1 hr. and then left at the room temperature for 3 days. The quaternary salt was precipitated by adding ethyl acetate and dry ether, and the yellow precipitate was collected, washed several times with anhydrous ether, and dried under vacuum. The crude salt (1.8 g.) was dissolved in 30 ml. of concd. hydrochloric acid and heated on the

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(22) W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5556 (1951).

(23) A small quantity of this compound was prepared earlier by Dr. Dieter Pawellek, working in this laboratory.

(24) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(25) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

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(10) K. Goto and Z. Kitasato, *J. Chem. Soc.*, 1234 (1930).

(11) J. S. Buck and W. H. Perkin, Jr., *J. Chem. Soc.*, 125, 1675 (1924).

(12) A. Pictet and A. Gams, *Ber.*, **44**, 2480 (1911).

(13) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 105, 1456 (1914).

(14) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 2783 (1948).

(15) E. Späth and P. L. Julian, *Ber.*, **64B**, 1131 (1931).

(16) Z. Kitasato, *Proc. Imp. Acad. Tokyo*, **2**, 124 (1926). *Brit. Chem. Abstr.*, 1160 (1926).

(17) Except as noted all melting points were determined on the Fisher-Johns block and are uncorrected. Infrared absorption spectra were determined by the potassium bromide plate method using the Perkin-Elmer model Infracord Spectrophotometer. All ultraviolet spectra were measured in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. silica cells. Except as noted all analyses were by Drs. Weiler and Strauss, Oxford, England.

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(19) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2797 (1950).

(20) R. I. T. Cromartie and J. Harley-Mason, *J. Am. Chem. Soc.*, **74**, 2525 (1952).

steam bath for 1 hr.<sup>26</sup> The acid was distilled and the red residue was carefully dried on a porous plate and then crystallized from methanol. The product was obtained as orange needles, m.p. 250° dec. (in sealed tube); yield, 1.6 g. (80%). The analytical sample melted at the same temperature;  $\lambda_{\max}$  246, 285, 328, 355, and 464  $\mu$ ; min., 268, 306, 344, and 404  $\mu$ .

*Anal.* Calcd. for  $C_{21}H_{20}O_4NBr$ : C, 58.60; H, 4.65; N, 3.25. Found: C, 58.83; H, 4.74; N, 3.26.

The *perchlorate* formed red needles from methanol, m.p. 310–312° dec. (sealed tube).

*Anal.* Calcd. for  $C_{21}H_{20}ClNO_5$ : C, 56.20; H, 4.45; N, 3.12. Found: C, 55.80; H, 4.60; N, 2.92.

**2,3,9,10-Tetramethoxydibenzo[a,g]quinolizidine (tetrahydropalmatine, X).** A solution containing 0.35 g. of the above dehydropalmatine bromide in 150 ml. of methanol, was hydrogenated at atmospheric pressure in presence of 50 mg. of platinum oxide. The solution was filtered from the catalyst and the filtrate was concentrated under vacuum, affording an almost colorless solid. This was dissolved in water, and ammonia was added to precipitate the base, which was extracted with ether. The ethereal solution was dried (magnesium sulfate) and the ether removed. The residue was crystallized twice from dilute methanol (Norit), when the ( $\pm$ )-tetrahydropalmatine (X) was obtained as colorless prisms, m.p. 147° (lit.,<sup>7</sup> m.p. 147°); yield, 152 mg. (53%). The base gave no depression of melting point when mixed with an authentic sample<sup>27</sup> and infrared spectra of the two were identical.

*Anal.* Calcd. for  $C_{21}H_{28}O_4N$ : C, 70.99; H, 7.04; N, 3.94. Found: C, 71.08; H, 7.04; N, 4.24.

The *hydrochloride*, prepared by passing hydrogen chloride into a dry ethereal solution of the base, was crystallized from methanol as colorless needles, m.p. 215–216° (lit.,<sup>28</sup> m.p. 215°).

**2,3-Dimethoxy-9,10-methylenedioxybenz[a]acridizinium chloride (dehydroepiberberinium chloride) (VI. X = Cl).** The oxime (XVII, 1 g.) was quaternized in the usual way with 2,3-methylenedioxybenzyl bromide<sup>25</sup> and the crude salt cyclized in concentrated hydrochloric acid. The product crystallized from a mixture of methanol and ethanol as orange needles, m.p. 275–277° dec. (sealed tube); yield 1.4 g. (80%);  $\lambda_{\max}$  248, 275, 327, 358, and 492; min. 262, 304, 340, and 417  $\mu$ .

*Anal.* Calcd. for  $C_{20}H_{16}ClNO_4 \cdot 2H_2O$ : C, 59.18; H, 4.93; N, 3.45. Found: C, 58.91; H, 4.63; N, 3.66.

The *perchlorate* was obtained in the usual way and crystallized from dimethylformamide and ethanol as scarlet red needles, m.p. 315–316° dec. (sealed tube).

*Anal.* Calcd. for  $C_{20}H_{16}ClNO_5$ : C, 55.36; H, 3.69; N, 3.23. Found: C, 55.11; H, 3.90; N, 3.16.

**2,3-Dimethoxy-9,10-methylenedioxydibenzo[a,g]quinolizidine (tetrahydroepiberberine, XI).** A suspension of 2,3-dimethoxy-9,10-methylenedioxybenz[a]acridizinium chloride (VI. X = Cl, 500 mg.) in methanol (200 ml.) was hydrogenated in presence of platinum oxide catalyst (80 mg.) for 24 hr. The crude free base (250 mg., 55%) was crystallized twice from ethanol and was obtained as colorless prisms, m.p. 167–168° (lit.,<sup>9,10</sup> m.p. 169–170°, 168°). A minute crystal was dissolved in glacial acetic acid to which a drop of concentrated sulphuric acid was added, giving a colorless solution which slowly turned violet. Tetrahydroepiberberine shows the same reaction.<sup>9,10</sup>

*Anal.* Calcd. for  $C_{20}H_{22}NO_4$ : C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55; H, 6.16; N, 4.22.

The *hydrochloride* crystallized from water as colorless needles which decomposed at 246°. The melting point could

not be raised by further crystallization (lit.<sup>10,29</sup> dec, about 286°; dec. 285–290°).

*Anal.*<sup>24</sup> Calcd. for  $C_{20}H_{21}O_4N \cdot HCl$ : C, 63.91; H, 5.85. Found: C, 63.95; H, 5.81.

**2,3-Dimethoxy-10,11-methylenedioxybenz[a]acridizinium chloride (dehydropseudoepiberberinium chloride, VII. X = Cl).** The quaternary salt, obtained from the oxime (XVII, 500 mg.) and 3,4-methylenedioxybenzyl bromide<sup>3,13</sup> in dimethylformamide, was cyclized in the usual way. The yellow product crystallized from excess methanol as greenish yellow microneedles, m.p. 278–280 dec. (sealed tube); yield 800 mg. (quantitative);  $\lambda_{\max}$  276, 309, 322, and 413; min. 250, 285, 317, and 367  $\mu$ .

*Anal.* Calcd. for  $C_{20}H_{16}ClNO_4 \cdot H_2O$ : C, 61.93; H, 4.64; N, 3.61. Found: C, 61.57; H, 4.54; N, 3.82.

**2,3-Dimethoxy-10,11-methylenedioxydibenzo[a,g]quinolizidine (tetrahydropseudoepiberberine, XII).** A suspension of the above salt in methanol was hydrogenated and the base obtained in the usual way was crystallized from dilute methanol as colorless needles, m.p. 160° (lit.,<sup>11</sup> m.p. 160–161°); yield, 225 mg. (55%).

*Anal.* Calcd. for  $C_{20}H_{21}NO_4$ : C, 70.78; H, 6.24; N, 4.13. Found: C, 70.85; H, 6.37; N, 4.20.

The *picrate* was prepared<sup>1</sup> the usual way, m.p. 150° dec. (lit.,<sup>11</sup> m.p. 149–150°).

**2,3,10,11-Tetramethoxybenz[a]acridizinium chloride (dehydronorcoralydine, VIII. X = Cl).** The oxime (XVII, 1 g.) quaternized easily with veratryl bromide (1 g.) in the presence of dimethylformamide (10 ml.) producing stout yellow prisms which, on cyclization for 10 min. with concentrated hydrochloric acid, afforded yellow crystals. These crystallized from methanol as fine yellow needles, m.p. 240–242° dec. (sealed tube); yield, 1.4 g. (75%);  $\lambda_{\max}$  278, 309, 322, 417; min. 250, 286, 318, and 370  $\mu$ .

*Anal.* Calcd. for  $C_{21}H_{20}ClNO_4 \cdot H_2O$ : C, 59.78; H, 5.69; N, 3.32. Found: C, 59.61; H, 5.60; N, 3.20.

The *perchlorate* was prepared in aqueous methanolic solution and was obtained as yellow needles from dimethylformamide, m.p. 367–368° dec. (sealed tube).

*Anal.* Calcd. for  $C_{21}H_{20}ClNO_5$ : C, 56.06; H, 4.44; N, 3.11. Found: C, 56.25; H, 4.69; N, 3.12.

**2,3,10,11-Tetramethoxydibenzo[a,g]quinolizidine (norcoralydine, XIII).** The above salt (VIII) was hydrogenated in the usual way and the colorless norcoralydine hydrochloride thus obtained was crystallized several times from dilute methanol as colorless prisms, m.p. 232° dec. (lit.,<sup>14,30</sup> m.p. 234–237° dec., 236–237°); yield 60%. The product gave no depression when mixed with an authentic sample<sup>31</sup> of hydrochloride.

*Anal.* Calcd. for  $C_{21}H_{25}NO_4 \cdot HCl$ : C, 63.39; H, 6.64; N, 3.83. Found: C, 63.33, 63.11; H, 6.57; 6.73; N, 3.63.

**2,3,10-Trimethoxybenz[a]acridizinium chloride (IX. X = Cl).** *m*-Methoxybenzylbromide (1.5 g.) was quaternized with the oxime (XVII, 1 g.) in presence of dimethylformamide and the quaternary salt was cyclized with concentrated hydrochloric acid. The yellow precipitate was crystallized from a mixture of ethanol and methanol. The product was obtained as yellow needles, m.p. 242 dec. (sealed tube); yield 1.2 g. (72%);  $\lambda_{\max}$  277, 312, 332, 435; min. 250, 300, 322, and 380  $\mu$ .

*Anal.* Calcd. for  $C_{20}H_{18}ClNO_3 \cdot CH_3OH \cdot \frac{1}{2}H_2O$ : C, 62.06; H, 5.66; N, 3.44. Found: C, 62.03; H, 5.94; N, 3.42.

The *perchlorate* was obtained as greenish yellow needles from methanol and ethanol, m.p. 310–311° dec. (sealed tube).

*Anal.* Calcd. for  $C_{20}H_{18}ClNO_7$ : C, 57.27; H, 4.30; N, 3.34. Found: C, 56.95; H, 4.41; N, 3.42.

**2,3,10-Trimethoxydibenzo[a,g]quinolizidine (XIV).** The above acridizinium chloride (IX) was hydrogenated with platinum oxide catalyst in methanol. The almost color-

(26) In subsequent experiments it was found that the cyclization time could be shortened to 10–20 min.

(27) We are indebted to Prof. Alfred Burger for the gift of this sample.

(28) K. Feist, *Arch. Pharm.*, **245**, 586 (1906).

(29) W. H. Perkin, Jr., *J. Chem. Soc.*, 113, 492 (1918).

(30) R. H. F. Manske, *Can. J. Research*, **16B**, 81 (1938).

(31) We are indebted to Professor D. S. Tarbell for the gift of a sample of the free base.

less product thus obtained was crystallized several times from dilute methanol (Norit) as colorless prisms, m.p. 214–215°; yield 50%.

*Anal.* Calcd. for  $C_{25}H_{23}NO_3 \cdot HCl \cdot H_2O$ : C, 63.24; H, 6.85; N, 3.68. Found: C, 63.21; H, 6.95; N, 3.65.

*2,3,9,10-Bismethylenedioxybenz[a]acridizinium chloride* (dehydrocoptisine chloride, II, X = Cl). A mixture of the oxime of 6,7-methylenedioxyisoquinoline 1-carboxaldehyde<sup>3</sup> (0.9 g.) 2,3-methylenedioxybenzylbromide<sup>4</sup> (1 g.) and dimethylformamide (15 ml.) was allowed to react in the usual way and the quaternary salt was cyclized with concentrated hydrochloric acid. The red precipitate was collected and crystallized from a mixture of ethanol and methanol as red needles, decomposing above 300° (sealed tube); yield 1.5 g. (85%);  $\lambda_{max}$  248, 317, 356, 490; min. 264, 294, 337, and 418 m $\mu$ .

The analytical sample was recrystallized from excess methanol, without change in melting point.

*Anal.* Calcd. for  $C_{19}H_{12}ClNO_4 \cdot 3/2 H_2O$ : C, 60.00; H, 3.94. Found: C, 59.69; H, 4.05.

The perchlorate was obtained as red needles from dimethylformamide and methanol, decomposing from 350°.

*Anal.* Calcd. for  $C_{19}H_{12}ClNO_8$ : C, 54.61; H, 2.87; N, 3.35. Found: C, 54.50; H, 3.21; N, 3.75.

*2,3,9,10-Bismethylenedioxydibenzo[a,g]quinolizidine* (tetrahydrocoptisine,  $\pm$ -stylopine, IV). The above salt (II, X = Cl) was hydrogenated in the usual way and the free base was crystallized twice from methanol. The tetrahydrocoptisine (XIV) was obtained as colorless needles, m.p. 217–218° dec. (lit.,<sup>9,15,16</sup> m.p. 219°, 227–228°, 215–216°); yield 50%. It was found that a solution of the base in glacial acetic acid slowly turned green on addition of a drop of concentrated sulfuric acid, while the further addition of a drop of dilute nitric acid produced a red color. Tetrahydrocoptisine was reported to behave similarly.<sup>9</sup>

*Anal.*<sup>24</sup> Calcd. for  $C_{19}H_{17}NO_4$ : C, 70.57; H, 5.30; N, 4.33. Found: C, 70.64; H, 5.14; N, 4.56.

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## Trimerization of Acetylenes

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The trimerization of monovinylacetylene and the cotrimerization of divinylacetylene with acetylene and with methylacetylene have been effected under mild conditions using triisobutylaluminum/titanium tetrachloride catalyst to give trivinylbenzenes and *o*-divinylbenzenes, respectively.

The thermal trimerization of acetylene to benzene was reported almost one hundred years ago by Berthelot.<sup>1</sup> Since then, such catalysts as metal carbonyls,<sup>2</sup> triphenylphosphinenickel carbonyl,<sup>3</sup> trialkylchromium,<sup>4</sup> diborane-activated silicaalumina,<sup>5</sup> and triisobutylaluminum-titanium tetrachloride<sup>6</sup> have been shown to facilitate the trimerization of acetylenes. Trialkylaluminum-titanium tetrachloride catalysts are well known for their ability to catalyze the polymerization of olefins,<sup>7</sup> and have been used to polymerize 1-hexyne to linear conjugated structures.<sup>8</sup>

Although vinylacetylenes might thus be expected to give complex products with trialkylaluminum-titanium tetrachloride catalysts, we have found that these catalysts promote trimerization of monovinylacetylene and cotrimerization of divinylacety-

lene with acetylene readily at –10 to 50° to give vinylbenzenes in modest to good yields.

At –10°, monovinylacetylene gave a mixture of 1,2,4- and 1,3,5-trivinylbenzenes in 74% yield. The yield at 50° was only 10%. The composition of this mixture as determined by ultraviolet analysis of the hydrogenated products was 90% 1,2,4-trivinylbenzene and 10% 1,3,5-trivinylbenzene. Statistically, one would expect a product containing 75% of 1,2,4-trivinylbenzene. 1,3,5-Trivinylbenzene has been prepared by another method,<sup>9</sup> but apparently the 1,2,4-isomer has not been reported.

The 1,2,4- and 1,3,5-trivinylbenzenes were separated by gas chromatography although considerable polymerization occurred on the column. The retention time of the 1,2,4-isomer was slightly shorter than that of the 1,3,5-isomer.

The infrared spectra of 1,3,5-trivinylbenzene and of the mixture of trivinylbenzenes were in general those expected for vinylbenzenes. The spectrum of 1,2,4-trivinylbenzene showed a strong band at 11.98  $\mu$  which was absent in the spectrum of 1,3,5-trivinylbenzene. As would be expected, the trivinylbenzenes absorb strongly in the ultraviolet,  $\lambda_{max}^{C_2H_5OH}$  246 m $\mu$  ( $\epsilon$  = 31,000).

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