m.p. 95–96°, $[\alpha]^{26}D$ +37.8 ± 0.7; ν_{max}^{Nujol} 3500 (OH); 3400 (amide NH); 1640 (amide C=O); 1520 (amide N); 720 (C—H of benzoate); and no ester C=O near 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.4; H, 7.46; N, 3.83. Found: C, 62.6; H, 7.64; N, 3.89.

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-4-O-mesyl-D-altritol (XIV).—To a solution of 1.12 g. (3.1 mmoles) of XIII in 8 ml. of reagent pyridine was added 0.5 ml. (6.6 mmoles) of mesyl chloride. After 24 hr. at room temperature protected from moisture, the mixture was poured into 100 ml. of ice–water saturated with sodium bicarbonate; the precipitate was collected, washed with water, and crystallized from methanol–ethyl acetate to yield 0.71 g. (52%) of XIV, m.p. 138–139°, and 0.22 g. (16%), m.p. 133–135°. The analytical sample had m.p. 134–136°; $[\alpha]^{26}D$ +24.7 ± 0.6; ν_{max}^{Nujol} 3450 (amide NH); 1645 (amide C=O); 1510 (amide NH); 1335, 1175 cm^{-1} (sulfonate).

Anal. Calcd. for $C_{20}H_{29}NO_8S$: C, 54.2: H, 6.60; N, 3.16; S, 7.21. Found: C, 54.4; H, 6.45; N, 3.32; S, 7.29.

In a repeat preparation starting with 2.2 g. of XIV, 0.015 g. of the oxazoline (XV) was isolated from the mother liquor.

3-Amino-3-N,4-O-benzo-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XV).—A mixture of 0.443 g. (1 mmole) of XIV, 0.33 g. (4 mmoles) of sodium acetate, and 3.3 ml. of 95% 2-methoxyethanol was heated under reflux for 19 hr. The mixture was diluted with 5 ml. of methylene dichloride and washed with water (2 × 10 ml.). The combined aqueous layers were back-extracted with 20 ml. of methylene dichloride and the combined organic extracts were then washed with 10 ml. of water. Dried over magnesium sulfate, the organic solution was evaporated to dryness *in vacuo* and the residue crystallized from methanol–water to yield 0.17 g. (49%) of XV, m.p. 86–88°; from the mother liquor was isolated XVIII, as described in the succeeding experiment.

Recrystallization of a similar preparation from methanol–water gave white crystals, m.p. 87–88°; $[\alpha]^{24}D$ −46.5 ± 0.4; ν_{max}^{Nujol} 1645 (C=N); 695 (benzoyl CH); and no OH—NH absorption at 3000–4000 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.27; N, 4.03. Found: C, 65.8; H, 7.21; N, 4.00.

When a solution of 100 mg. of pure XV in 4 ml. of 50% aqueous 2-methoxyethanol was refluxed for 24 hr., 3 mg. of XVIII could be isolated and 58 mg. of XV was recovered unchanged.

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XVIII). **(A) From XIV.**—The mother liquor from the 0.17 g. of the preceding preparation was diluted with 50 ml. of water and extracted with methylene dichloride (4 × 20 ml.). Dried with magnesium sulfate, the combined extracts were concentrated and the residue crystallized from petroleum ether–ethyl acetate to yield 0.090 g. (25%) of the benzamido iditol,[12] XVIII, m.p. 121–123°, $[\alpha]^{24}D$ +22.9 ± 0.3; ν_{max}^{Nujol} 3450 (shoulder), 3350, 3200 (OH, NH); 1650 (m), 1620 (s) (amide I); 1540 (s) (amide II); 715, 695 cm.$^{-1}$ (shoulder) (benzoyl CH).

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.6; H, 7.64; N, 3.89. Found: C, 62.5; H, 7.32; N, 3.94.

This compound was recovered unchanged when its solution in benzene was refluxed 3 hr., then evaporated on a steam bath. It was also recovered unchanged when its benzene solution was stirred with anhydrous cupric sulfate for 3 days.

An earlier preparation of XVIII melted at 109–111° and showed ν_{max}^{Nujol} 3500 (OH); 3300 (NH); 1625 (amide I); 1540 (amide II); 720, 695 cm.$^{-1}$ (benzoate CH). This form was not isolated again.[12]

(B) By O-Debenzoylation of XVII Obtained from X.—Debenzoylation of 0.045 g. (0.096 mmole) of XVII as described for the preparation of XIII, gave, after recrystallization from ethyl acetate–petroleum ether, 0.023 g. (65%) of pure product, m.p. 122–124°. The material was identical with preparation A as shown by mixed melting point and identical infrared spectra.

3-Benzamido-4-O-benzoyl-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XVII). **(A) From X.**—Benzoylation of 100 mg. (0.38 mmole) of X as described for the preparation of XII gave, after recrystallization from ethyl acetate–petroleum ether, 0.13 g. (72%) of white crystals, m.p. 162–164°, $[\alpha]^{24}D$ +63.1 ± 0.4; ν_{max}^{Nujol} 3300 (NH); 1710 (ester C=O); 1640 (amide I); 1545 (amide II); 715, 695 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.5; H, 6.67; N, 2.98. Found: C, 66.4; H, 6.86; N, 3.11.

(B) By Benzoylation of XVIII Obtained from XIV.—To a solution of 25 mg. (0.068 mmoles) of XVIII (m.p. 121–123°) in 1 ml. of reagent pyridine was added 0.05 ml. (0.44 mmoles) of benzoyl chloride. After 24 hr. at room temperature in a stoppered flask, the mixture was processed as described for XII. Two recrystallizations from ethyl acetate–petroleum ether gave 12 mg. (31%) of white crystals, m.p. 163–164°, that were identical with preparation A as shown by mixed melting point and infrared spectra.

Similarly, benzoylation of the low melting dimorph (109–111°) of XVIII gave the same dibenzoate, XVII.

3-Benzamido-3-deoxy-4-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XVI).—Treatment of a solution of 0.1 g. (0.38 mmole) of IX in 3 ml. of pyridine with 0.18 ml. (1.55 mmoles) of benzoyl chloride for 24 hr. at room temperature yielded, after recrystallization from ethyl acetate–petroleum ether, 0.125 g. (69%) of XVI, m.p. 133–135°. Further recrystallization gave the analytical sample, m.p. 138–139°; $[\alpha]^{24}D$ +45.8 ± 0.3; ν_{max}^{Nujol} 3390 (NH); 1710 (ester C=O); 1645 (amide I); 1525 (amide II); 730, 705 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.5; H, 6.67; N, 2.98. Found: C, 66.7; H, 6.84; N, 3.07.

Acknowledgment.—The authors thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by contract no. SA-43-ph-4346.

Vasicinone. A Bronchodilator Principle from *Adhatoda Vasica* Nees (N. O. Acanthaceae)

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Received July 18, 1961

A Bronchodilator principle "Vasicinone" has been isolated from *Adhatoda vasica* Nees (N. O. Acanthaceae) and its identity established with 2,3(α-hydroxytrimethylene)-4-quinazolone obtained by the oxidation of Vasicine. Vasicinone has also been found to be identical with an alkaloid recently isolated from *Peganum harmala* Linn. It is shown that Vasicine can be converted to Vasicinone by autoöxidation.

Adhatoda vasica Nees is an evergreen subherbaceous bush and is used in the indigenous medicine as a remedy for cold, cough, bronchitis, asthma, etc.

Hooper,[1] found in it, "a nonvolatile body" of the nature of an alkaloid, an organic acid "Adhatodic acid" and a steam volatile "odorous principle." Sen and Ghose[2] obtained an alkaloid "Vasicine" from its leaves. Chopra and Ghosh[3,4] found that Vasicine possesses a slight but persistent bronchodilator effect. Mithal

(1) D. Hooper, *Pharm. J.*, **18**, 841 (1888).

(2) J. N. Sen and T. P. Ghose, *J. Indian Chem. Soc.*, **1**, 315 (1924).

(3) R. N. Chopra and S. Ghosh, *Indian J. Med. Res.*, **13**, 205 (1925).

(4) R. N. Chopra and S. Ghosh, *Indian Med. Gaz.*, **60**, 354 (1925).

and Schroff[5] claimed to have isolated a new quaternary ammonium base from the leaves called "Vasicinine." This was, however, later found to be identical with Betaine.[6]

Different melting points of Vasicine and its hydrochloride have been reported in the literature.[2-4,7] This fact, together with the observation that pure Vasicine isolated in this laboratory showed a bronchoconstrictor effect, aroused our interest in the present work. On repeating the process of Mithal and Schroff (see ref. 5) we discovered another alkaloid[8,9] in the fraction said to contain Vasicine by them. The alkaloid was first isolated as a crystalline hydrochloride from which the crystalline base could be obtained easily. The new alkaloid has been named "Vasicinone." Subsequently, Vasicine and Vasicinone were isolated from the crude total alkaloids by countercurrent distribution and partition chromatography. The latter method was used as an analytical tool for quantitative estimation of Vasicine and Vasicinone in mixtures.

Microanalyses and molecular weight determination gave $C_{11}H_{10}N_2O_2$ as the molecular formula of Vasicinone. Obviously, Vasicinone must be an oxidation product of Vasicine ($C_{11}H_{12}N_2O$). Vasicine has been previously[10-12] oxidized with 30% hydrogen peroxide to a compound $C_{11}H_{10}N_2O_2$, the structure of which was established as 2,3 (α-hydroxytrimethylene)-4-quinazolone. Vasicine as well as the crude total alkaloids were oxidized with 30% hydrogen peroxide by us to give a compound which was found to be identical with Vasicinone.[13,9]

The crude total alkaloids contained predominantly Vasicine, but a gradual conversion of Vasicine to Vasicinone, probably due to autoöxidation was observed during experiments on countercurrent distribution and partition chromatography. Pure Vasicine could similarly be autoöxidized to Vasicinone.

Vasicinone isolated from the crude total alkaloids by partition chromatography was predominantly *l*-Vasicinone. Autoöxidation or oxidation with hydrogen peroxide gave a mixture of *l*- and *dl*-forms. A pure *dl*-form was at times obtained by the oxidation method. Pure *l*- and *dl*-forms could be separated from a mixture by taking advantage of the relatively lower solubility of *l*-Vasicinone hydrochloride in 5% hydrochloric acid. Both these forms were found to have a similar ultraviolet and infrared spectra and the same R_f value.

That Vasicine is present in the plant in the optically active form and is racemized during the process of isolation,[14] was confirmed by the isolation of *l*-Vasicine[15] under special conditions. The fact that the crude total alkaloids when oxidized yield *l*- and *dl*-forms of Vasicinone indicates that the racemization and oxidation take place side by side.

Paper chromatography using Whatman no. 1 filter paper and the solvent system butanol–acetic acid–water (10:1:5) gave 0.57–0.58 as R_f of Vasicine and 0.77–0.79 as that of Vasicinone.

We have isolated the alkaloids described by Koretskaya[16] from the seeds of *Peganum harmala* Linn., using a method different from that used by the Russian author. The alkaloid $C_{11}H_{10}N_2O_2$ has been found to be identical with Vasicinone.[9] In a later paper, Koretskaya and Utkin[17] also gave the structure of this alkaloid as 2,3 (α-hydroxytrimethylene)-4-quinazolone.

Pharmacological studies, which will be published elsewhere, show that both *l*- and *dl*-forms of Vasicinone are active bronchodilators, whereas Vasicine is a bronchoconstrictor.

Experimental

The leaves of *Adhatoda vasica* Nees used in this investigation were obtained from the market and were found to be genuine.

Crude Total Alkaloids.—Vasaka leaves in coarse powder (1.125 kg.) were refluxed with 90% alcohol (5.5 l.) for 1 hr. The extract was filtered and alcohol was removed under reduced pressure. The dark green mass (110 g.) obtained was extracted thrice with hot distilled water and the aqueous extract was filtered. The filtrate was extracted five times with chloroform to remove the coloring matter, then made alkaline with 5% caustic soda and repeatedly extracted with chloroform till free from alkaloids. The combined chloroform extracts were extracted with 5% hydrochloric acid till free from alkaloids. The acid solution was made alkaline with ammonia and alkaloids extracted with chloroform. After repeating this operation twice, the final chloroform extract was dried, filtered, and chloroform was removed under reduced pressure. Crude total alkaloids (8.0 g.) were obtained as a brown powder.

Vasicinone and Vasicine Hydrochlorides.—The crude total alkaloids (8 g.) on crystallization from 95% alcohol gave two types of crystals (5 g.) melting at about 180°. They were dissolved in boiling absolute alcohol, the solution was allowed to cool a little, and ethereal hydrochloric acid was added. The colorless needles of Vasicinone hydrochloride which crystallized out were filtered and dried (0.8 g.) m.p. 232–34° dec. The mother liquor when treated with dry ether till slight turbidity and allowed to stand at 15° for three days gave brown crystals of Vasicine hydrochloride (2 g.). From this, pure Vasicine hydrochloride was obtained by recrystallization from 95% alcohol, using animal charcoal for decolorizing. Anhydrous Vasicine hydrochloride melts at 208–209°.

Anal. Calcd. for $C_{11}H_{12}N_2O.HCl.2H_2O$: C, 50.67; H, 6.52; N, 10.74; Cl, 13.6. Found: C, 50.75; H, 6.6; N, 11.01; Cl, 13.42.

Vasicinone hydrochloride was not analyzed because of the possibility of hydrolysis.

Vasicinone Base from the Hydrochloride.—Vasicinone base was obtained from Vasicinone hydrochloride (0.8 g.) by dissolving in acidified water and adjusting the pH to about 5 with ammonia when colorless needles of Vasicinone base separated on standing (0.4 g.) The mother liquor when extracted with chloroform, yielded another crop of Vasicinone (0.15 g.). The total quantity (0.55 g.) of Vasicinone was recrystallized from 95% alcohol, m.p. 200–201° $[\alpha]^{22}D$ −100 (0.5% in chloroform).

The ultraviolet spectrum of Vasicinone (concn. 10 μg./ml. in water) shows maxima at 227, 272, 302, and 315 mμ.

The shorter wave part of the infrared spectra shows bands at 3.21, 3.42, 6.03, 6.875, 7.22, 7.516, 7.743, 8.275, 8.48, 9.06, 9.265, 9.73, 10.13, 10.312, 11.155, 11.33, 11.54, 11.71, 12.92, 13.352, 13.89, and 14.41 μ.

Anal. Found: C, 65.33; H, 4.93; N, 13.65; O, 16.09. Molecular weight (Rast) was about 215 (only one reading was taken). Molecular formula, therefore, was $C_{11}H_{10}N_2O_2$.

Vasicine Base from the Hydrochloride.—Vasicine hydrochloride (2 g.) was dissolved in water and ammonia was added.

(5) B. M. Mithal and M. L. Schroff, *Indian Pharmacist*, **9**, 307 (1954).
(6) B. M. Mithal and D. W. Mathieson, *J. Pharm. Pharmacol.*, **9**, 344 (1957).
(7) A. K. Dey and J. N. Ray, *J. Indian Chem. Soc.*, **4**, 541 (1927).
(8) A. H. Amin and D. R. Mehta, Indian Patent 62349 (November 21, 1957); *Chem. Abstr.*, **54**, 829f (1960).
(9) A. H. Amin and D. R. Mehta, *Nature*, **184**, 1317 (1959).
(10) T. P. Ghose, S. Krishna, K. S. Narang, and J. N. Ray, *J. Chem. Soc.*, 2740 (1932).
(11) T. P. Ghose, S. Krishna, K. S. Narang, and J. N. Ray, *Current Sci.*, **4**, 158 (1935).
(12) R. C. Morris, W. E. Hanford, and R. Adams, *J. Am. Chem. Soc.*, **57**, 951 (1935).
(13) D. R. Mehta, Indian Patent 64603 (July 9, 1958); *Chem. Abstr.*, **54**, 20096f (1960).
(14) E. Späth and F. Kuffner, *Ber.*, **68B**, 1384 (1935).
(15) E. Späth and F. Kesztler, *ibid.*, **69B**, 384 (1936).
(16) N. I. Koretskaya, *Chem. Abstr.*, **52**, 9163d (1958).
(17) N. I. Koretskaya and L. M. Utkin, *ibid.* **52**, 18501c (1958).

TABLE I

Substance autoöxidized	Quantity, g.	Solvent and its volume, ml.	Period of exposure, days	Weight of Vasicinone, g.	Weight of Vasicine, g.
Crude total alkaloids	0.2500	Chloroform 10	None	0.0800	0.173
Crude total alkaloids	.2500	Chloroform 10	7	.2170	.0324
Vasicine	.1004	Chloroform 10	None	.0003	.9990
Vasicine	.1004	Chloroform 10	25	.1025	.0129
Vasicine	.1021	Benzene 30	25	.1164	.0036
Vasicine	.0999	Ethylene dichloride 10	25	.1140	.0069

The white precipitate obtained was filtered, dried and crystallized from 95% alcohol, m.p. 196–98°. It was found to be optically inactive. In one of the experiments, Vasicine was obtained in optically active form as a microcrystalline powder; $[\alpha]^{29}D$ −177 (1.74% in chloroform).

Countercurrent Distribution.—The solvent system 10% acetic acid and chloroform[18] was found suitable for the distribution. Crude total alkaloids (3 g.) was subjected to eight transfers in nine separating funnels. The lower chloroform phase was moved. From the two phases the base was isolated in each case by the usual method. The eighteen residues thus obtained were all characterized by paper chromatography as described earlier. Vasicine (1.75 g.) was found in the acid phase of the first three funnels and Vasicinone (0.776 g.) in the last three funnels. Residues from other funnels were negligible and impure and hence rejected.

Partition Chromatography.—The crude total alkaloids (1 g.) was dissolved in moist chloroform (6 ml.) and put on top of a partition column of 10 g. Hyflo Supercel containing 5 ml. of 10% phosphoric acid. Elution was carried out with moist chloroform till the eluate did not extract any more alkaloid (0.38 g. residue of Vasicinone). The elution was then continued with ammoniacal chloroform till the eluate did not give test for alkaloids (0.6 g. residue of Vasicine). These residues were characterized as Vasicinone and Vasicine, respectively, by paper chromatography.

Purification of the Bases over Alumina.—The crude Vasicine and Vasicinone fractions obtained by countercurrent distribution and partition chromatography were dissolved in dry chloroform, and the solution passed through alumina. Crude Vasicine (1.75 g.) and crude Vasicinone (0.776 g.) from the countercurrent distribution gave pure substances (1.5 and 0.7 g., respectively). Similarly, crude Vasicine (0.6 g.) and crude Vasicinone (0.38 g.) from partition chromatography gave pure substances (0.5 and 0.3 g., respectively). Pure Vasicinone thus obtained was crystallized from hot 95% alcohol, m.p. 201–202° $[\alpha]^{22}D$ −90 (0.5% in chloroform). Pure Vasicine was converted into the hydrochloride, base liberated from it, and then crystallized, m.p. 195–196°. It was optically inactive.

Oxidation of Vasicine with Hydrogen Peroxide.—Pure Vasicine (1 g.) was dissolved in a mixture of 30% hydrogen peroxide (5 ml.) and acetone distilled over potassium permanganate (7 ml.), the solution warmed (about 50°) for 15 min. and kept overnight. Crystals of 2, 3 (α-hydroxytrimethylene)-4-quinazolone obtained were crystallized from hot 95% alcohol (0.4 g.) m.p. 212–213°. It was found to be identical with Vasicinone. It was optically inactive.

Oxidation of Crude Total Alkaloids with Hydrogen Peroxide.—Crude total alkaloids (5 g.) when oxidized by the method described above gave a crystalline product (3.7 g.) which on recrystallization from 80% alcohol gave pure substance (3 g.) melting between 200 and 212°. The m.p. was not depressed when mixed with pure Vasicinone, $[\alpha]^{29}D$ −58 (0.5% in chloroform).

Autoöxidation of Crude Total Alkaloids and Vasicine.—Crude total alkaloids and Vasicine were separately dissolved in chloroform and the solutions exposed to strong daylight. Benzene and ethylene dichloride could also be used as solvents. A longer period of exposure to light was required in case of Vasicine because of the dull light in the rainy season when oxidation of Vasicine was carried out. From these samples Vasicine and Vasicinone were quantitatively estimated by partition chromatography. The results are given in Table I.

Later it was possible to prepare bigger quantities of Vasicinone on a preparative scale from crude total alkaloids by autoöxidation giving a mixture of *l*- and *dl*- Vasicinone.

Separation of *l*- and *dl*-Vasicinone.—A sample of Vasicinone (4 g.) with an optical rotation of $[\alpha]^{29}D$ −58 (0.5% in chloroform) was dissolved in 5% hydrochloric acid (25 ml.), allowed to stand overnight, and the crystals of Vasicinone hydrochloride (A) filtered out the next day. The mother liquor (B) was preserved for further work. The crystals of Vasicinone hydrochloride (A) (1.98 g.) melting at 230–231° dec. were dissolved in acidified water, ammonia added to the filtrate to bring the pH to about 4.5, and left overnight. The crystals of Vasicinone were filtered out; (1.1 g.), $[\alpha]^{28}D$ −100 (0.5% in chloroform). The mother liquor (B) was treated with ammonia to bring the pH to about 3, left overnight, Vasicinone filtered out (1.9 g.), and crystallized from 80% alcohol giving optically inactive substance. *l*-Vasicinone melted at 201–202° and *dl*-Vasicinone at 211–212°.

Isolation of Vasicinone from *Peganum Harmala*.—The crushed seeds (250 g.) were extracted twice with 90% alcohol (600 ml.) and filtered. Alcohol was removed under reduced pressure and the sirupy residue (33 g.), extracted with 25% acetic acid (250 ml.) and filtered. The filtrate was treated with ether (300 ml.) to remove color. The acid extract was made alkaline with ammonia and alkaloids extracted with chloroform (1200 ml.). The chloroform extract was again extracted with 25% acetic acid (800 ml.) till free from alkaloids. The operation was repeated once more and the final chloroform extract (1 l.) was dehydrated and chloroform removed from the filtrate to give a brown residue of crude total alkaloids (9.76 g.).

The crude total alkaloid was subjected to partition chromatography, the conditions being the same as in the partition chromatography of crude alkaloids of *Adhatoda vasica*. The moist chloroform eluate gave 0.228 g. alkaloid and ammoniacal chloroform eluate gave 8.7 g. alkaloid. The alkaloid from the moist chloroform eluate gave two spots on filter paper corresponding to Vasicinone and trimethylene-4-quinazolone, while the alkaloid from ammoniacal chloroform gave spots of Harmine, Harmaline,[19] and Vasicine. The alkaloidal residue from moist chloroform eluate put on a column of florisil, gave a pink band and the bottom of the column was yellow. Elution was carried out with chloroform (400 ml.) till the yellow colored part was completely eluted (0.11 g.). Elution was then continued with chloroform (500 ml.) till the pink band was completely eluted (0.076 g.). Both these residues were identified as trimethylene-4-quinazolone and Vasicinone respectively by paper chromatography. Vasicinone was converted into its hydrochloride as done previously (50 mg.) m.p. 229–230° dec., and base liberated from it (25 mg.) m.p. 201–202°, $[\alpha]^{29}D$ −74 (0.5% in chloroform). It is therefore a mixture of *l*- and *dl*-forms. Mixed melting point with pure *l*-Vasicinone was not depressed and its ultraviolet spectrum was identical with that of Vasicinone.

Salts of Vasicinone.—The preparation of Vasicinone hydrochloride has already been described in the process of isolation of Vasicinone.

The other salts were prepared by dissolving Vasicinone in methanol, adding the calculated quantity of the appropriate acid, evaporating to dryness and crystallizing from absolute alcohol. The sulphate, nitrate, hydriodide, and hydrobromide of Vasicinone all melt with decomposition at 182–185°, 138–139°, 222–226°, and 254–255°, respectively.

Double Chlorides of Vasicinone with Gold and Platinum.—Vasicinone hydrochloride (0.1 g.) was dissolved in acidulated water and a solution of gold chloride (0.17 g.) added. An orange liquid separated, which solidified on putting in an ice bath. The solid was dissolved in 2% hydrochloric acid and left overnight for crystallization; yield, 0.14 g.

Anal. Calcd. for B.H. $AuCl_4$: Au, 36.35; Found: Au, 36.66.

(18) H. A. Nash and R. M. Broker, *J. Am. Chem. Soc.*, **75**, 1942 (1953).

(19) F. A. Hochstein and A. M. Paradies, *ibid.*, **79**, 5735 (1957).

The double chloride of Vasicinone and platinum was prepared as above using Vasicinone hydrochloride (0.1 g.) and platinic chloride (0.095 g.). The crude substance was crystallized from 2% hydrochloric acid.

Anal. Calcd. for $B_2.H_2PtCl_4$: Pt, 23.9; Found: Pt, 23.9.

Acknowledgment.—The authors are indebted to Dr. A. H. Amin, Director of Research, Alembic Chemical Works Co. Ltd., for his kind interest and encouragement.

Acetylenic Amines. V. Morpholines from Substituted N-(2-Hydroxyalkyl)-propargylamines

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Received August 22, 1962

Various methods of preparing substituted N-(2-hydroxyalkyl)propargylamines and their cyclization and subsequent hydrogenation to various morpholine derivatives are reported. Facile hydration of 2-methylenemorpholines to the 2-hydroxy-2-methylmorpholines has been noted.

The base-catalyzed cyclization of N-(2-hydroxyalkyl)propargylamines (III. $R^1 = R^3 = H$) has been reported[1] to give oxazolidines (IV) instead of the expected morpholines (V). In our laboratories, however, it has been possible to prepare the morpholines (V) from compounds of the type III where both R and R^1 are alkyl or aryl, as shown in Fig. 1.

The ready availability[2,3] of the 1,1-disubstituted propargylamines (I) suggested their use as starting materials. It was found that they could be converted to the desired β-amino alcohols (III) by several methods. The reactions of I with ethylene oxide and substituted ethylene oxides could usually be accomplished, although the conditions necessary for the reactions to proceed needed to be varied. Since the reaction of substituted ethylene oxides always gave the 2-substituted-2-hydroxyethylamines (III), 1-substituted 2-hydroxyethylamines were obtained by the treatment of the amines with the appropriate α-halo ketones or esters followed by reduction with sodium borohydride or lithium aluminum hydride. Under the proper conditions, the reduction of the esters or ketones with lithium aluminum hydride or sodium borohydride proceeded with little or no attack at the acetylenic group.

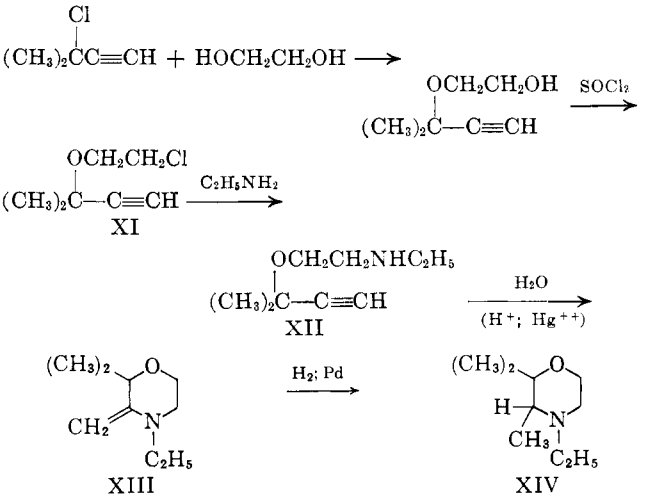
The base-catalyzed cyclization of these β-amino alcohols, where both R and R^1 are alkyl or aryl, gave the 2-methylenemorpholines (V) which could be readily hydrogenated to the 2-methylmorpholines (X). Treatment of V with dry hydrogen chloride under anhydrous conditions gave the hydrochloride salts. However, in the presence of water, hydration took place, and the 2-hydroxy-2-methylmorpholine (VI) was produced.

This compound (VI) was identical to that obtained by the treatment of the substituted N-(2-hydroxyalkyl)propargylamines (III) under conditions necessary for hydration[3] of the acetylenic amine.

The structure assigned to X was proved by an unequivocal synthesis. The β-hydroxyethylamine (VIII) was treated with ethylene oxide to form the aminodiol (IX). Cyclization of this compound under acidic conditions gave a compound identical to that obtained by hydrogenation of the 2-methylenemorpholine. Reduction of the 2-hydroxymorpholine (VI. $R = R^1 = CH_3$; $R^2 = C_2H_5$), with lithium aluminum hydride gave as one of the products a compound identical to the aminodiol (IX).

Substitution of chlorine for the terminal acetylenic hydrogen did not prevent cyclization since 1-chloro-3-(N-ethyl-N-2-hydroxyethylamino)-3-methyl-1-butyne[4] cyclized to the 2-(chloromethylene)morpholine.

For comparison purposes, the isomer XIV was prepared by means of the hydrogenation of XIII. Compound XIII was obtained by the acid-catalyzed cyclization of XII, which could be readily prepared from the chloro compound XI, as shown above.



The infrared and n.m.r. spectra were consistent with the assigned structures. The 2-methylenemorpholines gave intense absorption peaks in the infrared at 6 μ.

The stereochemistry of the hydroxymorpholines (VI), the morpholines (X), and the diols (IX), where $R \neq H$ or $R' = R$, has not been elucidated. The products, as isolated, appeared to be relatively pure materials and no evidence of isomers was encountered. The question of whether the same or different isomers of IX and X are produced by the different synthetic routes is being investigated.

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