The alkaloids of Alstonia barks. Pt. 2, A. macrophylla, Wall; A. somersetensis, F.M. Bailey; A. verticillosa, F. Muell; A. villosa, Blum / by T.M. Sharp.

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THE ALKALOIDS OF ALSTONIA BARKS. PART II. *A. MACROPHYLLA*, WALL; *A. SOMERSETENSIS*, F. M. BAILEY; *A. VERTICILLOSA*, F. MUELL; *A. VILLOSA*, BLUM.

BY

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265. *The Alkaloids of* Alstonia *Barks. Part II.* A. macrophylla, *Wall.*, A. somersetensis, *F. M. Bailey*, A. verticillosa, *F. Muell.*, A. villosa, *Blum.*

By Thomas M. Sharp.

The search for anti-malarial drugs in the genus *Alstonia* (Part I, this vol., p. 287) has been continued by the examination of four more species. *A. somersetensis*, *A. verticillosa*, and *A. villosa* are Australian species, the last occurring also in Java, whilst *A. macrophylla* is a native of Malaya and the Philippine Islands. Of these, the first two do not appear to have been examined before, but the other two are known to contain alkaloids, and in particular not to contain echitamine, the characteristic alkaloid of a number of African and other *Alstonias* (Goodson, J., 1932, 2626).

A. verticillosa contains a considerable amount of a mixture of sterols the separation of which has not been attempted, and in addition a small amount of echitamine. It is very similar to " dita-bark " (*A. scholaris*) examined many years ago by Jobst and Hesse (*Annalen*, 1875, **178**, 49). The other three barks all contain, in addition to much amorphous base, an alkaloid which forms well-defined crystalline salts and for which the name *villalstonine* is suggested, as it was first isolated from *A. villosa*. *A. macrophylla* contains, besides villalstonine, three other alkaloids, for which the names *macralstonine*, *macralstonidine*, and base M are suggested. The last is present in exiguous amount. Macralstonidine is also present in *A. somersetensis*, and a new base, isolated in comparatively small amount, and provisionally named base V, has been obtained from *A. villosa*.

Villalstonine, $C_{40}H_{50}O_4N_4$, has two basic and two non-basic nitrogen atoms, forms

salts of the general formula B,2HA, and yields a *dimethiodide*. It contains one methoxy- and two methylimino-groups, and this precludes the possibility of the simpler formula $C_{20}H_{24(26)}O_2N_2$. It forms, moreover, a *mono*-N-*benzyl* derivative, and final confirmation of the more complex formula is afforded by molecular-weight determination cryoscopically in benzene. The methoxy-group appears to exist as a methyl ester, since hydrolysis with alcoholic potassium hydroxide furnishes an amphoteric *substance*, $C_{39}H_{48}O_4N_4$, which does not contain a methoxy-group. The other bases are present in much smaller amounts. Macralstonine, $C_{44}H_{52}O_5N_4$, is crystalline and forms a crystalline *sulphate* but has not yielded any other crystalline salt. The base is very sparingly soluble in the common organic solvents except pyridine and chloroform, and has one methoxy- and three methylimino-groups. It is noteworthy that the optical rotation of the base and sulphate are opposite in sign, as is the case, *e.g.*, with aconitine and emetine. Its molecular weight has not been confirmed by direct determination owing to the lack of a suitable solvent, but the methoxyl content and phytochemical considerations leave little doubt as to its complexity. Macralstonidine, $C_{41}H_{50}O_3N_4$, is crystalline and forms crystalline salts. It is soluble in most organic solvents, contains two methylimino-groups but no methoxy-group, and appears to have a dioxymethylene group since it gives a red colour with Gaebel's reagent. Satisfactory molecular-weight determinations could not be obtained; it appears to be associated in benzene. Alkaloids M and V are crystalline, but owing to the very small quantity available neither formulæ nor names are suggested for them. The formulæ put forward for macralstonine and macralstonidine are to be regarded as provisional, for, although the analytical figures are in good agreement with those suggested, it is desirable to have more derivatives in order definitely to establish formulæ of such complexity. All the new alkaloids described give colour reactions characteristic of indole derivatives. The high molecular weight of these alkaloids is reminiscent of recent work on a number of *iso*quinoline alkaloids such as emetine, and more especially oxyacanthine, *iso*chondodendrine, curine, etc., which were at first thought to contain one *iso*quinoline group, but are now known to contain two such nuclei, and of calycanthine which is now considered to contain two indole nuclei.

Pharmacological experiments have been carried out with villalstonine hydrochloride by Dr. A. C. White of the Wellcome Physiological Research Laboratories. He found that a concentration of 1 : 6,500 to 1 : 12,500 caused a slight increase in the movement of the isolated rabbit uterus; a concentration of 1 : 25,000 had no action on the isolated guinea-pig uterus, and 1 : 50,000 none on the isolated rabbit intestine; a dose of 2 mg. per kg. caused, in the anæsthetised cat, a fall in blood pressure, which was unaffected by atropine. This fall was less than that caused by the same dose of alstonine sulphate. The action on bird malaria has not yet been determined. The other alkaloids have not been tested, as they occur in too small amount to be of practical importance.

The genus *Alstonia* is widely distributed throughout the tropical parts of the Old World and Australia and, with the exception of a small number of species occurring in China and New Caledonia, representative species have now been examined from all the districts from which it has been reported (for literature, see Part I, and Goodson and Henry, J., 1925, **127**, 1640). The alkaloids which have been isolated fall into three groups represented by (*a*) echitamine, occurring in many species from Africa, the East Indies, and Australia, (*b*) villalstonine, from a number of Australian and East Indian species, and (*c*) alstonine, which has only been found in one species, *viz.*, *A. constricta* from Australia. These three types of alkaloid appear to have little in common except that both villalstonine and echitamine appear to be indole derivatives, whilst alstonine does not give any of the usual indole colour reactions.

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Experimental.

The barks were finely ground and, with the exception of *A. verticillosa*, which required a preliminary extraction with petroleum, exhausted with alcohol. The alcoholic solutions were

divided into convenient-sized batches, and concentrated to the consistency of thick syrups, extracted with sufficient cold 0·5% sulphuric acid to render the solutions faintly acid to Congo-red, filtered, diluted with an equal volume of water, filtered again from precipitated impurities, and worked through by appropriate methods as described below.

A. macrophylla.—The acid liquor was extracted with ether to remove impurities, made strongly alkaline with sodium carbonate and shaken with ether. During this process a large amount of buff to greyish-green, granular, amorphous solid separated and formed a middle layer on standing. After a few extractions, the solid was collected by filtration and reserved (A), and the clear filtrate exhausted with ether. Occasionally the early ethereal extracts deposited crystals which were collected; when none appeared, the ether, after drying, was concentrated and left over-night. The colourless crystals which separated were filtered off, and consisted of crude macralstonine mixed with base M. The filtrate was evaporated and the residual resinous base converted into oxalate and dissolved in alcohol. From this solution, villalstonine oxalate separated in an almost pure condition, and a further, less pure, amount was obtained on concentration. After standing until no more oxalate separated, the solution was evaporated, the residue dissolved in water, treated with potassium carbonate, and shaken with ether. A portion of the liberated base failed to dissolve in ether, and was obtained by subsequent extraction with chloroform. After evaporation and solution in dry alcohol, both the ether-soluble and the chloroform-soluble part deposited crude macralstonidine as a colourless, crystalline powder. An additional quantity of this base was also obtained after conversion of the amorphous residue into perchlorate, and recovery of the base in the usual manner. The amorphous solid A (above) was dried in a desiccator, mixed with half its weight of powdered quick-lime, and exhausted in a Soxhlet extractor with benzene. The benzene solution was extracted with *N*-sulphuric acid, and the acid liquor basified with sodium carbonate and extracted with ether. This solution on concentration deposited macralstonine, and the filtrate after evaporation and solution in dry alcohol furnished macralstonidine. A further small amount of each of these bases was obtained by extraction of the residue from the benzene extracts with chloroform. The yields of the alkaloids from all the barks are given in the following table; the figures in parentheses are percentage yields.

Bark.	*A. macrophylla.*	*A. villosa.*	*A. somersetensis.*	*A. verticillosa.*
Weight, kg.	53·5	4·58	3·45	3·0
Total base, g.	496 (0·93)	66·4 (1·45)	47·8 (1·39)	8·0 (0·27)
Villalstonine oxalate, g.	216·9 (0·405)	19·7 (0·43)	3·05 (0·088)	—
Macralstonine, g.	18·8 (0·035)	—	—	—
Macralstonidine, g.	21·6 (0·0407)	—	2·13 (0·062)	—
M. sulphate, g.	1·03 (0·0019)	—	—	—
Base V, g.	—	0·65 (0·014)	—	—
Echitamine HCl, g.	—	—	—	4·7 (0·16)

A. villosa.—Macralstonine was not isolated from this bark, but apart from this, the method for the isolation of villalstonine oxalate was the same as that described above. The residual amorphous oxalate was converted into the more soluble sulphate, and its aqueous solution treated with 10% sodium perchlorate solution so long as a precipitate formed. This precipitated perchlorate failed to yield any crystalline substance. The filtrate was made alkaline with sodium carbonate and extracted with ether; this solution on standing for a short time deposited crystals of base V, which were collected, and a further small amount was obtained from the filtrate. The amorphous granular solid corresponding with A (see above) was extracted with dilute sulphuric acid, basified with sodium carbonate, and extracted with ether. After conversion into oxalate, it furnished a small amount of villalstonine oxalate together with amorphous material.

A. somersetensis.—The process described for the isolation of alkaloids from the two previous barks was not applicable to this bark owing to the formation of persistent and intractable emulsions. The acid solution of the alkaloids was treated with excess of sodium carbonate, the slimy precipitate filtered off, dried in a desiccator, and exhausted with ether (Soxhlet). On evaporation, this left a syrupy base which was made into oxalate but failed to crystallise. Villalstonine was obtained, however, after conversion into hydrobromide. The amorphous part was converted into the more soluble sulphate, and treated with sodium perchlorate. The base recovered from the precipitated perchlorate deposited crystals of macralstonidine after solution in dry alcohol.

A. verticillosa.—This bark (3 kg.) was exhausted with petroleum (b. p. 60—80°), the marc

air-dried, and then extracted with industrial methylated spirit. The petroleum extract on evaporation left a yellowish elastic mass (228·5 g.) which was partly soluble in alcohol; the residue from this extraction was grey and of a rubbery consistency, with physical properties very similar to those of Hesse's echikautschin (*loc. cit.*), although not necessarily identical with it. The alcoholic solution deposited colourless crystals which were obviously mixtures and gave colorations characteristic of sterols with Liebermann's reagent. No further attempt at purification was made. One crop of crystals appeared homogeneous and had the same m. p. as lupeol, but a mixed m. p. showed a depression of about 40°. The methylated spirit extract was evaporated to dryness, the residue treated with sufficient 0·25% sulphuric acid to remove the alkaloid, and the acid liquor extracted with ether. It was then treated with 25% sodium hydroxide solution and shaken with chloroform. From this solution, the crude alkaloid was obtained as sulphate by extraction with *N*-sulphuric acid and evaporation to dryness (yield 9·12 g.). This contained a little alkaloid which could be liberated from its salts by sodium carbonate; it was, therefore, dissolved in water, made alkaline with sodium carbonate, and extracted with chloroform. This gave 0·6 g. of dark-coloured varnish, from which nothing crystalline could be obtained and which corresponds with Jobst and Hesse's ditamine from *A. scholaris*. The aqueous liquor was then treated with sodium hydroxide and chloroform, the chloroform concentrated to a small volume, mixed with alcohol, and acidified to methyl-red with 10% hydrochloric acid. Almost at once, the solution gave a crystalline crop of echitamine hydrochloride (4·7 g.).

Villalstonine.—The *oxalate* was purified by crystallisation from alcohol, separating in colourless leaflets, m. p. 235° * (decomp.). The salt from *A. villosa* had $[\alpha]_D$ + 31·2°, that from *A. macrophylla* $[\alpha]_D$ + 32·1° (c = 0·56 in acetone), † $[\alpha]_D$ + 55·6° (c = 0·5 in water) [Found, on dried material, (*a*) from *A. macrophylla*: C, 67·8, 67·7; H, 6·95, 6·9; N, 7·8, 7·7; OMe, 4·2; NMe, 6·3; (*b*) from *A. villosa*: C, 67·8, 67·8; H, 7·1, 7·0; N, 7·6, 7·7; OMe, 4·2; NMe, 6·4. $C_{40}H_{50}O_4N_4,C_2H_2O_4$ requires C, 68·1; H, 7·1; N, 7·6; OMe, 4·2; 2NMe, 7·8%]. The *hydrochloride*, prepared by the addition of freshly prepared alcoholic hydrogen chloride to dry alcoholic solution of the base, formed colourless needles, m. p. 270° (decomp.), $[\alpha]_D$ + 56·3° from *A. villosa*, + 56·1° from *A. somersetensis* (c = 0·5 in water) (Found: loss at 120° in a vacuum, 9·8. $C_{40}H_{50}O_4N_4,2HCl,4H_2O$ requires $4H_2O$, 9·1. Found, on dried salt: C, 66·2, 66·2; H, 7·4, 7·35; N, 7·5, 7·5; Cl, 9·7, 9·7; OMe, 4·2, 4·5; NMe, 6·9, 8·1. $C_{40}H_{50}O_4N_4,2HCl$ requires C, 66·4; H, 7·25; N, 7·75; Cl, 9·8; OMe, 4·3; 2NMe, 8·0%). The dried salt rapidly absorbs moisture from the air (Found: gain on exposure to air, 10·35. Calc. for $4H_2O$: 10·0%).

An aqueous solution of the hydrochloride or other salt of villalstonine slowly becomes pink on keeping. The *sulphate* does not crystallise easily. It is rather sparingly soluble in alcohol and crystallises only after concentration, forming small prismatic rods, which do not melt at 310°, $[\alpha]_D$ + 52·94° (c = 1·02 in water) (Found: loss at 110° in a vacuum, 12·7. $C_{40}H_{50}O_4N_4,H_2SO_4,6H_2O$ requires $6H_2O$, 12·6%. Found on dry salt: C, 63·3, 63·2; H, 6·85, 6·95; N, 7·7, 7·55; S, 4·3, 4·3; OMe, 4·1, 4·1; NMe, 6·3, 6·35. $C_{40}H_{50}O_4N_4,H_2SO_4$ requires C, 64·1; H, 7·0; N, 7·5; S, 4·3; OMe, 4·1; 2NMe, 7·8%). On exposure to air the dry salt absorbs 13·4% of its weight (Calc. for $6H_2O$: 14·4%). The *hydrobromide*, prepared by precipitation, crystallised from alcohol in colourless needles, m. p. 293° (decomp.) (Found: loss at 110° in a vacuum, 8·0. $C_{40}H_{50}O_4N_4,2HBr,4H_2O$ requires $4H_2O$, 8·15%. Found, on dry salt: C, 59·4, 59·5; H, 6·3, 6·3; N, 7·1, 7·0; Br, 19·2, 19·3; OMe, 4·0, 3·8; NMe, 7·3, 6·8. $C_{40}H_{50}O_4N_4,2HBr$ requires C, 59·1; H, 6·5; N, 6·9; Br, 19·7; OMe, 3·8; 2NMe, 7·2%). On exposure to air the dry salt absorbed $4H_2O$ (Found: gain on exposure, 8·8. Calc.: 8·9%). The *hydriodide*, colourless balls of needles from methyl alcohol, m. p. 286° (decomp.), showed a tendency to become yellow on recrystallisation and failed to give satisfactory analytical figures (Found, on salt dried at 110° in a vacuum: C, 54·2; H, 5·8; N, 6·2; I, 26·7; OMe, 3·4; NMe, 5·7. $C_{40}H_{50}O_4N_4,2HI$ requires C, 53·0; H, 5·8; N, 6·2; I, 28·0; OMe, 3·4; 2NMe, 6·4%). The *base* was obtained as a colourless granular powder on the addition of sodium carbonate or hydroxide to an aqueous solution of the pure hydrochloride. It was very soluble in most organic solvents and was not obtained in a crystalline condition. For analysis it was triturated with many changes of water, and dried at 100° in a vacuum. It sintered at 218° and slowly melted up to 260° [Found: C, 73·5, 73·7; H, 7·6, 7·6; N, 8·6, 8·4; OMe, 4·8, 4·6; NMe, 7·9, 8·1; *M*, cryoscopic in benzene, using alumina as drying agent (Roberts and Bury, J., 1923, **123**, 2037; Brown and Bury, J., 1924, **125**, 2219), 657, 645, 651. $C_{40}H_{50}O_4N_4$ requires C, 73·8; H, 7·75; N, 8·6; OMe, 4·8; 2NMe, 8·9%; *M*, 650·4). The *dimethiodide* was prepared by

* All m. p.'s are corrected.

† All the rotations were done on the dry salts.

treating the base (0·5 g.) with methyl iodide (1·5 c.c.). After standing over-night, the excess of methyl iodide was distilled off, and the residue dissolved in methyl alcohol, from which it crystallised in rosettes of stout needles, which became pink on keeping, m. p. 287° (decomp.) (Found, on substance dried at 110°: C, 54·4, 54·3; H, 6·1, 6·1; N, 5·9, 5·9; I, 26·7; OMe, 3·5, 3·4; NMe, 12·5, 12·7. $C_{40}H_{50}O_4N_4,2CH_3I$ requires C, 53·95; H, 6·0; N, 6·0; I, 27·2; OMe, 3·3; 4NMe, 12·4%). The *mono-N-benzyl* derivative was formed by heating the base (0·6 g.) with benzyl chloride (3 c.c.) for ½ hour on a water-bath. The red-brown solution was poured into water (30 c.c.), extracted with ether to remove excess of benzyl chloride, made alkaline with sodium carbonate, and shaken with chloroform. After drying, the chloroform solution was shaken with very dilute hydrochloric acid and then with water. Both the aqueous and the chloroform layer on evaporation left behind the same substance, which crystallised from chloroform in colourless prisms, m. p. 246° (decomp.) (yield 0·59 g.) (Found, on substance dried at 110°: C, 69·4, 69·25; H, 7·0, 6·9; N, 7·0, 6·9; Cl, 8·0; OMe, 3·5, 3·3; NMe, 7·3, 7·05. $C_{40}H_{50}O_4N_4,C_7H_7Cl,HCl$ requires C, 69·35; H, 7·2; N, 6·9; Cl, 8·8; OMe, 3·8; 2NMe, 7·1%). An aqueous solution gave a precipitate with sodium carbonate, but not with sodium hydroxide solution. Villalstonine base (2 g.) was boiled under reflux with 10% alcoholic potassium hydroxide for 8 hrs., the solution diluted with water, the alcohol evaporated, and unchanged base (0·45 g.) removed by extraction with ether. After the addition of excess of ammonium chloride, the solution was continuously extracted with ether for 2 days. This removed a base (0·63 g.) which was suspended in alcohol and acidified with alcoholic hydrogen chloride. The solid dissolved, and later separated in a crystalline condition. After recrystallisation from dry alcohol it had m. p. 291—293° (decomp.). It easily loses hydrogen chloride on recrystallisation (Found, on salt dried at 100° in a vacuum: C, 66·5, 66·3; H, 7·2, 7·4; N, 7·9, 7·9; Cl, 9·2, 9·0; OMe, nil; NMe, 6·5, 6·3. $C_{38}H_{47}O_2N_4\cdot CO_2H,2HCl$ requires C, 66·0; H, 7·1; N, 7·9; Cl, 10·0; 2NMe, 8·2%). The base separated from dry alcohol in an amorphous condition; it was soluble in sodium carbonate solution, from which it could not be extracted by ether.

Macralstonine.—The crude macralstonine was boiled with absolute alcohol to remove admixed villalstonine and amorphous alkaloid, and the residue extracted with acetone (Soxhlet). The base slowly dissolved, and accumulated in a crystalline condition in the receiver. It was collected from time to time, and finally recrystallised by solution in cold pyridine and addition of an equal volume of dry alcohol. It thus formed colourless rectangular rods, m. p. 293° (decomp.), $[\alpha]_D$ + 27·5° (c = 1·008 in chloroform). The *base* is very soluble in chloroform and pyridine, sparingly soluble in acetone, and almost insoluble in other organic solvents (Found, on base dried at 105° in a vacuum: C, 73·4, 73·3; H, 7·4, 7·5; N, 7·8, 7·9; OMe, 5·2, 5·2; NMe, 13·2, 13·3. $C_{44}H_{54}O_5N_4$ requires C, 73·5; H, 7·6; N, 7·8; OMe, 4·3; 3NMe, 12·1%). The *sulphate* crystallised from methyl alcohol in bright prismatic rods which became opaque at once when filtered off, and melted indefinitely at about 263° (decomp.), $[\alpha]_D$ − 36·8° (c = 1·022 in water) (Found, on dry salt: C, 64·5, 64·5; H, 7·0, 7·0; N, 6·9, 6·95; S, 3·85, 3·8. $C_{44}H_{54}O_5N_4,H_2SO_4$ requires C, 64·7; H, 6·9; N, 6·9; S, 3·9%). Consistent results could not be obtained in the methoxy- and methylimino-determinations.

Sulphate of Base M.—The acetone filtrate from the purification of macralstonine was evaporated, the residue extracted with ether (Soxhlet), and the solution filtered from a little macralstonine which collected in the flask. The ether-soluble base was then converted into oxalate, the oxalate boiled with acetone, and the acetone-soluble part converted into sulphate. This salt crystallised from a large volume of alcohol in bipyramids with an indefinite m. p. about 257°, $[\alpha]_D$ − 71·9° (c = 0·98 in water). The quantity was too small for a thorough investigation.

Macralstonidine.—The *base* was easily purified by fractional crystallisation from dry alcohol. It formed colourless platelets which became yellow on the surface on exposure to light. It becomes vitreous on heating, and evolves gas at an indefinite temperature near 270°, $[\alpha]_D$ + 174·5° (c = 1·02 in benzene) (Found, on base dried at 105° in a vacuum: C, 75·8, 75·7; H, 7·7, 7·6; N, 8·4, 8·4; OMe, 0·7; NMe, 10·2, 10·3. $C_{41}H_{50}O_3N_4$ requires C, 76·1; H, 7·8; N, 8·7; 2NMe, 9·0%). The dried base is hygroscopic. The *hydrochloride* crystallised slowly from dry alcohol in rosettes of soft colourless needles, which became coloured on keeping, m. p. 326° (decomp.), $[\alpha]_D$ + 136·5° (c = 1·09 in water) (Found, on salt dried at 105° in a vacuum: C, 68·2, 68·25; H, 7·2, 7·0; N, 7·7, 7·6; Cl, 9·5, 9·65; OMe, nil; NMe, 9·95, 10·1. $C_{41}H_{50}O_3N_4,2HCl$ requires C, 68·4; H, 7·3; N, 7·8; Cl, 9·9; 2NMe, 8·1%).

Base V.—This base crystallised from alcohol in prisms, m. p. 273° (decomp.), $[\alpha]_D$ + 54·6° (c = 0·5 in chloroform). The quantity was insufficient for a more detailed study.

The colour reactions of the above alkaloids are given in the following table.

Alkaloid.	Vanillin–alcoholic HCl.	Gaebel's reagent.	Glyoxylic reagent.	Conc. HNO_3.	Conc. H_2SO_4.
Villalstonine	Immediate pink colour, gradually becomes blue-violet	Reddish-brown	Not characteristic	Greenish-yellow	Brown, changing through purple to blue
Macralstonine	Pale yellow, changes to orange and finally to brownish-pink	Brown	Not characteristic	Yellow	Yellowish-green, becoming yellow
Macralstonidine	No colour for some hours, gradually becomes pink	Red	Not characteristic	Yellow	No colour at first; becomes blue then pink
Base V	No colour for some hours, pink after 24 hours	Yellow	Pink ring	Red	No colour
Sulphate of base M	No immediate colour, amethyst after some hours	Reddish-brown	Not characteristic	Yellow	Yellowish-brown, changing to yellow

The echitamine hydrochloride from *A. verticillosa* was recrystallised from water until the m. p. and specific rotation remained constant. It then had m. p. 293—295° (decomp.), alone or admixed with an authentic specimen of echitamine hydrochloride; $[\alpha]_D$ — 58·8° (c = 1·003 in water) (recorded $[\alpha]_D$ — 54·3°). It gave a pure blue colour with Hopkins and Cole's glyoxylic reagent, a magenta colour with vanillin–hydrochloric acid, and a bright red coloration with strong nitric acid (Found, on dry salt: C, 62·9, 63·0; H, 7·0, 7·0; N, 6·6, 6·6; Cl, 8·7, 8·5. Calc. for $C_{22}H_{28}O_4N_2$,HCl: C, 62·8; H, 6·95; N, 6·7; Cl, 8·4%).

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