84. Ormosia *Alkaloids. Part II.*[1] *Dasycarpine.*

By R. T. Clarke and M. F. Grundon.

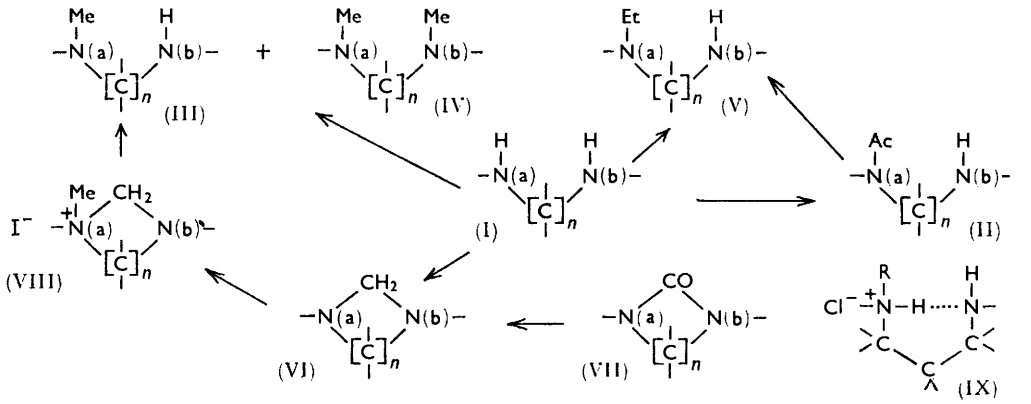
Dasycarpine affords *N*-acetyl, *N*-methyl, and *NN*-dimethyl derivatives, and forms intramolecular products with formaldehyde and carbonyl chloride. Various interconversions are described, and structural implications are discussed.

Dasycarpine, $C_{20}H_{35}N_3$, was shown previously [1] to contain three basic nitrogen atoms, at least one being present in a secondary amino-group. It is now apparent that dasycarpine (I) contains two secondary amino-groups [$\rangle$N(a)H and $\rangle$N(b)H]. Thus, reaction of dasycarpine with acetic anhydride and pyridine at room temperature gave in 81% yield a crystalline compound, $C_{22}H_{37}N_3O$, shown by its infrared absorption at 3450 and 1625 cm.$^{-1}$ to be a mono-*N*-acetyl derivative (II) containing a secondary amino-group.

Methylation of dasycarpine with methyl iodide afforded two crystalline products and

[1] Clarke and Grundon, *J.*, 1960, 41, is regarded as Part I.

an amorphous fraction. The major crystalline compound, $C_{21}H_{39}I_2N_3$, was a dihydriodide salt converted by sodium hydroxide into the corresponding base $C_{21}H_{37}N_3$, m. p. 120—121°. The base is an *N*-methyldasycarpine (III) since it contains a methylamino-group (nuclear magnetic resonance maximum at $\tau = 7{\cdot}82$) and a secondary-amino-function ($\nu_{max.}$ 3400 cm.$^{-1}$). The first overtone of the N–H stretching band in piperidine occurs at 6494 cm.$^{-1}$. Dasycarpine and *N*-methyldasycarpine absorb in the same region of the near-infrared, and the molecular extinction coefficients of the N–H bands (1·0 and 0·5, respectively) are a further indication of the presence of two secondary amino-groups in dasycarpine and one in *N*-methyldasycarpine. The amorphous fraction from the methylation experiment was probably a mixture of hydriodide salts. Treatment with sodium hydroxide gave a



compound, $C_{22}H_{39}N_3$, m. p. 116—117°, and more *N*-methyldasycarpine. The new compound was *NN*-dimethyldasycarpine (IV) since it showed no infrared absorption in the 3700—3200 cm.$^{-1}$ region; analysis confirmed the presence of two methylamino-groups. *NN*-Dimethyldasycarpine was also prepared by methylation of *N*-methyldasycarpine with methyl iodide. The second crystalline compound, $C_{22}H_{41}I_2N_3$, from the dasycarpine–methyl iodide reaction was obtained in very small yield. It is possibly a hydriodide *N*-methyldasycarpine methiodide, as an aqueous solution gave no precipitate with sodium hydroxide. The predominant methylation products of dasycarpine are therefore *N*-methyldasycarpine (47%) and *NN*-dimethyldasycarpine (14%).

Dasycarpine reacted more slowly with ethyl iodide; after 48 hr. *N*-ethyldasycarpine, $\nu_{max.}$ 3400 cm.$^{-1}$ (NH), was obtained as an oil, and was characterised as its trihydrobromide. The same *N*-ethyldasycarpine (V) resulted from reduction of *N*-acetyldasycarpine (II) with lithium aluminium hydride, showing that one secondary amino-group [N(a)H] of dasycarpine reacted preferentially with acetic anhydride and with ethyl iodide, and, by analogy, with methyl iodide. Isomeric monoacetylation or monoalkylation products were not isolated in any experiments and were not detected by paper chromatography.

Dasycarpine and formaldehyde at room temperature gave an almost quantitative yield of a compound, $C_{21}H_{35}N_3$ (VI), formed by an intramolecular reaction involving both secondary amino-groups, as shown by a molecular weight determination (mass-spectrometry) and by the absence of infrared absorption in the NH region. The formaldehyde compound was stable to cold acid, and gave a crystalline dihydrobromide. Hydrolysis with boiling hydrochloric acid was followed by paper chromatography; dasycarpine was detected after 4 hr., but the reaction was incomplete after 42 hr. In contrast, other derivatives of diaminomethane, for example methylene-*NN'*-dipiperidine [2] and hexahydropyrimidine [3] are easily hydrolysed by acid. The ready formation of the formaldehyde

[2] Ehrenburg, *J. prakt. Chem.*, 1887, (2), **36**, 117.
[3] Titherley and Branch, *J.*, 1913, **103**, 330.

compound and its remarkable stability suggest that dasycarpine has a favourable conformation for reaction with formaldehyde to form a new five- or six-membered ring.

An intramolecular reaction also occurred when dasycarpine was treated with carbonyl chloride, but the product (VII), was not sufficiently stable for analysis. Its structure was indicated by the absence of NH absorption in its infrared spectrum and by its reduction with lithium aluminium hydride to the formaldehyde compound (VI). Since the amide-carbonyl absorption of compound (VII) occurs at 1630 $cm.^{-1}$, the new ring is unstrained and likely to be six-membered. Dasycarpine therefore probably has structure (I; $n = 3$).

Dasycarpine is obviously related structurally to piptanthine from *Piptanthus nanus* M. Pop. Eisner and Šorm showed [4] that piptanthine has the formula $C_{20}H_{35}N_3$, contains two secondary amino-groups, and reacts with formaldehyde and with carbonyl chloride as does dasycarpine. The isolation of C-20 alkaloids from *Ormosia panamensis* Benth.[5] and *Ormosia jamaicensis* Orb.[6] has also been reported.

Earlier analyses of dasycarpine indicated the absence of an *N*-methyl group,[1] but a duplicate Herzig–Meyer determination and a similar analysis of the formaldehyde compound gave positive results (37% and 23% of the theoretical value for one methylamino-group, respectively). However, we do not consider that either of these compounds has a methylamino-group since their nuclear magnetic resonance spectra, unlike the spectrum of *N*-methyldasycarpine, do not have strong singlets in the 7·8 τ region. Lycorine,[7] aspidospermine,[8] and quebrachamine [9] are other alkaloids that give spurious results in the Herzig–Meyer determination.

The tertiary nitrogen of dasycarpine is not easily quaternised, as shown by the predominant formation of tertiary bases in the reaction with methyl iodide. Methiodides are formed from certain dasycarpine derivatives, but quaternisation apparently ocurs at new tertiary centres created by substitution at the secondary amino-group. The formaldehyde compound (VI) affords a monomethiodide that is given the partial stucture (VIII) since heating the corresponding quaternary hydroxide leads not to elimination but to the formation of *N*-methyldasycarpine (III). By analogy, the formation of a monomethiodide from *NN*-dimethyldasycarpine also involves reaction at N(a). Apparently dasycarpine, like certain other Leguminosae alkaloids, contains a shielded tertiary nitrogen atom. Matridine, for example, possesses two tertiary amino-groups but furnishes only a monomethiodide.[10] The secondary amino-group of tetrahydrodeoxycytisine reacted with methyl iodide to give *N*-methyltetrahydrodeoxycytisine hydriodide, the tertiary nitrogen being unaffected; a monomethiodide was formed from *N*-methyltetrahydrodeoxycytisine by quaternisation of the methylamino-group only.[11]

Dasycarpine monohydrochloride was prepared almost quantitatively from dasycarpine and one mol. of hydrochloric acid; it was identical with the crystalline compound (originally called alkaloid I[1]) obtained, probably as an artifact, during isolation of the alkaloids. The failure of the monohydrochloride to react with methyl iodide may be due to stabilisation by hydrogen bonding, perhaps as in (IX; R = H). The presence of an intermediate of similar structure (IX; R = Me) might account for the slow conversion of dasycarpine into *NN*-dimethyldasycarpine. In contrast, this dimethyldasycarpine was formed rapidly under the same conditions from *N*-methyldasycarpine, in which strong intramolecular hydrogen bonding is less likely.

[4] Eisner and Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2348.
[5] Lloyd and Horning, *J. Amer. Chem. Soc.*, 1958, **80**, 1506.
[6] Hassall and Wilson, *Chem. and Ind.*, 1961, 1359.
[7] Kondo and Tomimura, *J. Pharm. Soc., Japan*, 1928, **48**, 36.
[8] Conroy, Brook, Rout, and Silverman, *J. Amer. Chem. Soc.*, 1958, **80**, 5178.
[9] Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559.
[10] Tsuda and Mishima, *Chem. and Pharm. Bull. (Japan)*, 1957, **5**, 285.
[11] Freund and Horkheimer, *Ber.*, 1906, **39**, 814.

Experimental

M.p.s were taken on a Kofler block. Paper chromatography was on Whatman No. 1 paper in solvents A, B, and C of Lloyd and Horning; [5] spots were detected with the Dragendorff reagent.

Dasycarpine.—Dasycarpine, obtained as described previously,[1] was an oil, R_F 0·55 in solvent A, 0·47 in solvent B, and 0·73 in solvent C (Found: *N*-Me, 3·4. Calc. for $C_{20}H_{35}N_3$: *N*-Me, 9·1%).

N-*Acetyldasycarpine.*—Dasycarpine (750 mg.) in pyridine (5 c.c.) and acetic anhydride (2 c.c.) was kept at room temperature for 12 hr., added to ice, and the solution made strongly alkaline with sodium hydroxide. The precipitate of N-*acetyldasycarpine* formed plates (675 mg., 81%), m. p. 155—157° (from ethanol), R_F 6·61 in solvent A (Found: C, 73·3; H, 10·2; N, 11·6. $C_{22}H_{37}N_3O$ requires C, 73·5; H, 10·3; N, 11·7%).

Reaction of Dasycarpine with Methyl Iodide.—A solution of dasycarpine (1·0 g.) in methyl iodide (5 c.c.) was kept at room temperature for 12 hr., and evaporated. Trituration of the residue with methanol gave N-*methyldasycarpine methiodide hydriodide*, separating from methanol in prisms (0·11 g.), m. p. 246—247° (decomp.) (Found: C, 44·1; H, 7·3. $C_{22}H_{41}I_2N_3$ requires C, 43·9; H, 6·9%).

The methanol solution, obtained after removal of the methiodide, was evaporated. Trituration of the residue with ethanol gave a *dihydriodide* (0·55 g.), needles (from ethanol), m. p. 299—301° (decomp.) (Found: C, 43·1; H, 6·7; N, 7·4. $C_{21}H_{39}I_2N_3$ requires C, 43·0; H, 6·7; N, 7·2%). Paper chromatography in solvent A gave a single spot, R_F 0·42.

A solution of the dihydriodide in water was made alkaline with sodium hydroxide, and the precipitate of N-*methyldasycarpine* crystallised from aqueous ethanol in needles, m. p. 120—121°, R_F 0·43 in solvent A (Found: C, 76·0; H, 11·3. $C_{21}H_{37}N_3$ requires C, 76·1; H, 11·2%). The nuclear magnetic resonance spectrum in chloroform, tetramethylsilane being used as an internal standard, showed a singlet at $\tau = 7{\cdot}82$.

After removal of the dihydriodide, the ethanol solution was evaporated, and the residue in water was made alkaline with sodium hydroxide. Extraction with ether and evaporation of the ether gave a residue which afforded NN-*dimethyldasycarpine* in prisms (0·14 g.), m. p. 116—117° (from ethanol) (Found: C, 76·6; H, 11·3; *N*-Me, 13·4. $C_{22}H_{39}N_3$ requires C, 76·5; H, 11·4; 2*N*-Me, 16·8%).

After *NN*-dimethyldasycarpine had been removed, dilution of the ethanol solution with water gave needles (0·16 g.), m. p. 115—118°, identical (mixed m. p. and infrared spectrum) with *N*-methyldasycarpine.

Conversion of N-*Methyldasycarpine into* NN-*Dimethyldasycarpine.*—*N*-Methyldasycarpine (35 mg.) in methyl iodide (1 c.c.) was kept at room temperature for 12 hr., and the solution was evaporated. The residue, in water, was made alkaline with sodium hydroxide and extracted with ether. Evporation of the ether solution and crystallisation of the residue from ethanol afforded prisms (18 mg.), m. p. 115—117°, identical (mixed m. p. and infrared spectrum) with *NN*-dimethyldasycarpine.

NN-*Dimethyldasycarpine Methiodide.*—A solution of *NN*-dimethyldasycarpine (0·24 g.) in methyl iodide (5 c.c.) was kept at room temperature for 48 hr., and evaporated. A solution of the residue in water was made alkaline with sodium hydroxide and extracted with ether. The aqueous solution, when concentrated to 5 c.c., gave the *methiodide* (0·08 g.), crystallising from ethanol–ether in needles, m. p. 208—209° (decomp.) (Found: C, 56·7; H, 8·3. $C_{23}H_{42}IN_3$ requires C, 56·7; H, 8 6%).

N-*Ethyldasycarpine.*—(*a*) A solution of dasycarpine (100 mg.) in ethyl iodide was kept at room temperature for 24 hr., and evaporated. The residue was treated with aqueous sodium hydroxide and extracted with ether. Evaporation and distillation of the residue gave N-*ethyldasycarpine* as an oil, b. p. 180—185° (bath)/0·05 mm. (Found: C, 76·7; H, 11·3; N, 12·1. $C_{22}H_{39}N_3$ requires C, 76·5; H, 11·4; N, 12·2%).

The *hydrobromide* separated from ethanol in needles, m. p. 266—269° (decomp.) (Found: C, 42·9; H, 7·4; N, 7·0. $C_{22}H_{42}Br_3N_3,H_2O$ requires C, 43·4; H, 7·3; N, 7·0%).

(*b*) A solution of *N*-acetyldasycarpine (200 mg.) in ether was treated with excess of lithium aluminium hydride in ether, and the solution was refluxed for 3 hr. After the addition of aqueous sodium hydroxide, the ether solution was evaporated and the residue converted into

N-ethyldasycarpine hydrobromide, separating from ethanol in needles, m. p. 267—270° (decomp.), identical (mixed m. p. and infrared spectrum) with the sample obtained in (*a*).

Reaction of Dasycarpine with Formaldehyde.—A solution of dasycarpine (317 mg.) in glacial acetic acid–water (1 : 4) containing 30% formalin (0·2 c.c.) was kept at room temperature for 24 hr., made alkaline with sodium hydroxide, and extracted with ether. Evaporation of the ether, and trituration of the residue with light petroleum (b. p. 40—60°), gave the *formaldehyde compound* (320 mg., 97%), crystallising from ethanol in prisms, m. p. 143—144°, $[\alpha]_D$ +15° ($CHCl_3$), R_F 0·32 in solvent A, 0·41 in solvent B, and 0·67 in solvent C [Found: C, 76·7; H, 10·8; N, 13·1; *N*-Me, 2·0%; *M* (mass spectrometry), 328. $C_{21}H_{35}N_3$ requires C, 76·6; H, 10·6; N, 12·8; *N*-Me, 8·8%; *M*, 329].

The *hydrobromide*, prepared in ethanol with hydrobromic acid and precipitated by the addition of ether, crystallised from ethanol–ether in needles, m. p. 292—294° (decomp.) (Found: C, 49·1; H, 7·7; N, 7·9. $C_{21}H_{35}N_3,2HBr,H_2O$ requires C, 49·3; H, 7·6; N, 8·2%).

The formaldehyde compound (10 mg.) was refluxed with 6N-hydrochloric acid (4 c.c.). Hydrolysis to dasycarpine (R_F 0·54 in solvent A) was followed by paper chromatography. In the following Table the + signs show approximately the relative quantities of starting material and product.

Time (hr.)	0	2·75	4	17·5	41·5
R_F in solvent A	0·34	0·33	0·33	0·32+++	0·33+++
	—	—	0·54 (trace)	0·50+	0·54++

Conversion of the Formaldehyde Compound into N-*Methyldasycarpine.*—The formaldehyde compound was converted, with methyl iodide in methanol at room temperature, into its *methiodide*, separating from ethanol–ether in needles, m. p. 206—208° (Found: C, 55·2; H, 8·2; N, 8·5. $C_{22}H_{38}IN_3$ requires C, 55·8; H, 8·1; N, 8·9%).

The methiodide (100 mg.) in water (220 c.c.) was added to an ion-exchange resin (Amberlite IRA–400, OH^- form). Elution with water, and evaporation of the eluate gave a solid residue (60 mg.) which was heated at 160—180°/0·05 mm. The glassy sublimate crystallised in needles (45 mg., 64%), m. p. 118—119°, identical (mixed m. p. and infrared spectrum) with *N*-methyldasycarpine.

Reaction of Dasycarpine with Carbonyl Chloride.—A solution of carbonyl chloride in benzene was added slowly to dasycarpine (100 mg.) in chloroform (10 c.c.) at 5°. After 15 min. excess of aqueous sodium hydroxide was added, and the mixture was extracted with ether. Evaporation of the ether solution gave a colourless solid (95 mg.) which rapidly became red. Reduction of the product with lithium aluminium hydride afforded a gum that did not crystallise but was shown to be the formaldehyde compound by comparison of infrared spectra and by paper chromatography in solvents A, B, and C.

Dasycarpine Monohydrochloride.—(*a*) The *hydrochloride* (previously [1] called alkaloid I) crystallised from ethanol–ether or ethyl acetate in needles, m. p. 205—207° (decomp.), R_F 0·56 in solvent A, 0·48 in solvent B, and 0·73 in solvent C (Found: C, 65·2; H, 10·0; N, 11·1; Cl, 9·9. $C_{20}H_{36}ClN_3,H_2O$ requires C, 64·8; H, 10·3; N, 11·3; Cl, 9·6%). When an aqueous solution of the hydrochloride was treated with sodium hydroxide the oil obtained with ether was dasycarpine (comparison of infrared spectra).

(*b*) A solution of dasycarpine (51 mg.) in ether was treated with N-hydrochloric acid (0·16 c.c.; 1 equiv.). Addition of ether gave the hydrochloride, crystallising from ethanol–ether in needles (54 mg.), m. p. 206—207°, identical (mixed m. p. and infrared spectrum) with a sample described in (*a*).

Near-infrared Spectra.—By using a Perkin-Elmer model 21 instrument and a lithium fluoride prism, the spectra were determined with 2% chloroform solutions in a 1 cm. cell. In the following compounds the figures refer to the position of the first overtone of the N–H stretching band, and, in parentheses, to the molecular extinction coefficient (ε): dasycarpine, 6506 (1·0); *N*-methyldasycarpine, 6464 $cm.^{-1}$ (0·5). Piperidine absorbed at 6494 $cm.^{-1}$.

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