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STUDIES ON INDIAN MEDICINAL PLANTS—XIV*

INTERRELATIONSHIPS AMONG THE QUINAZOLINE ALKALOIDS FROM *GLYCOSMIS ARBOREA* (ROXB.) DC†

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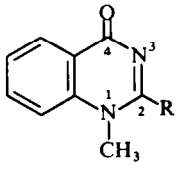
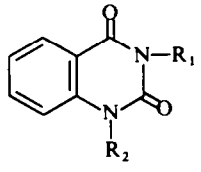
Abstract—Methylation and demethylation of the quinazoline alkaloids from *Glycosmis arborea* (Roxb.)DC. has been studied. Glycorine (I) and arborine (IV) may be demethylated to 4-quinazolone (V) and glycosminine (III) respectively. On remethylation with alkaline methyl iodide, V yielded almost exclusively the 3-methyl-(IV) while III gave a mixture of its 1-methyl-(IV) and the hitherto unreported 3-methyl-(VII) derivative. Oxidation of arborine with chromic oxide in acetic acid yielded glycorine and glycosmicine (II). The biogenetic significance of these observations is discussed.

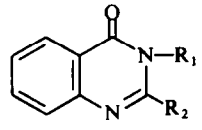
THE structures of glycorine (I), glycosmicine (II), glycosminine (III)[1] and arborine (IV),[2] the quinazolone alkaloids from *Glycosmis arborea*[3] exist in equilibrium forms.[1] The methylation and demethylation characteristics of the appropriate alkaloids with a view to correlating them biogenetically has now been investigated.



I: R = H
IV: R = $-CH_2Ph$



II: $R_1 = H$, $R_2 = Me$
X: $R_1 = R_2 = H$
XI: $R_1 = Me$, $R_2 = H$



III: $R_1 = H$, $R_2 = -CH_2Ph$
V: $R_1 = R_2 = H$
VI: $R_1 = Me$, $R_2 = H$

The hydrochlorides of glycorine and arborine on vacuum sublimation above their m.ps yielded 4-quinazolone (V) and glycosminine respectively by demethylation. On remethylation either with sodium and methyl iodide[4] or with formaldehyde and formic acid,[5] V did not reform glycorine except in trace amounts detectable only by TLC but afforded almost exclusively its 3-methyl derivative VI as would be expected[6] of a predominantly keto-dihydro structure of 4-quinazolone. On the other hand, glycosminine with alkaline methyl iodide furnished a mixture of its 1-methyl derivative (arborine) in 10% yield and a new base, m.p. 95°, as the major product (50%) better characterized as hydrochloride, m.p. 224° or picrate, m.p. 179°. The

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latter was inferred to be the hitherto unreported 3-methyl derivative VII of glycosminine from the methods of preparation since N-3 is known[6,7] to be preferentially alkylated in such compounds and from the spectral characteristics (*vide infra*).

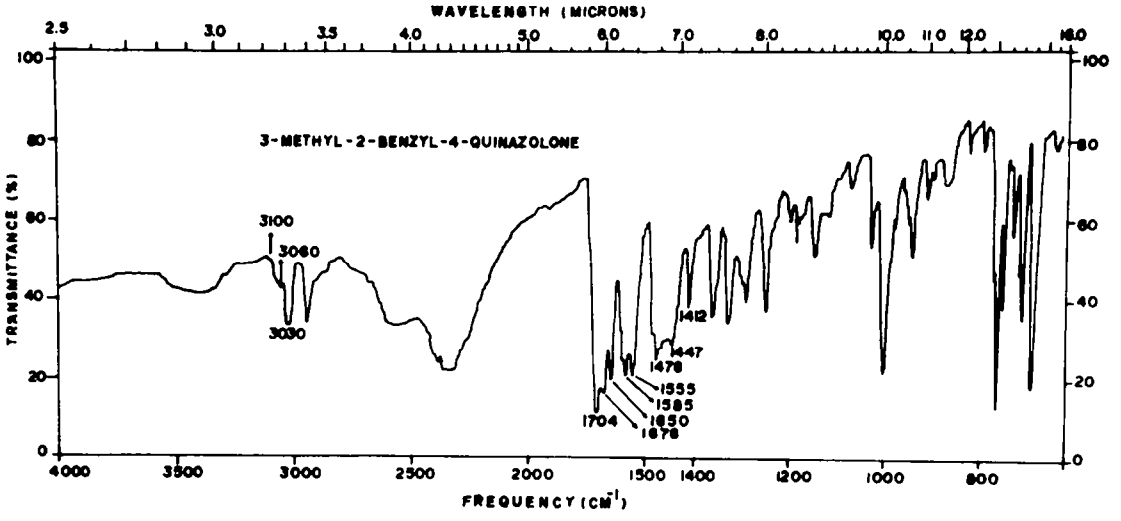


FIG. 1.

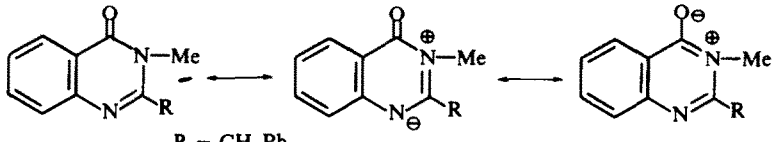
The UV absorption pattern of VII in ethanol very closely resembles that of glycosminine analogous to the spectroscopic similarity of quinazoline with its 3-methyl derivative (Table 1). The IR spectrum (Fig. 1) of the hydrochloride of VII in KBr besides showing the absence of the NH peak of glycosminine at 3356 cm^{-1} (2·98 μ)

TABLE 1. EFFECT OF METHYLATION AT DIFFERENT NITROGEN ATOMS OF 4-QUINAZOLONE ON UV ABSORPTION IN EtOH

Name of the compound	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε
4-Quinazolone (V)[6]	313	3·54	300	3·60	—	—	265	3·81	223	4·36
1-Methyl-4-quinazolone (I)[1]	317	3·84	306	3·91	278	3·66	269	3·59	230	4·08
3-Methyl-4-quinazolone (VI)[6]	313	3·46	301	3·56	276	3·82	267	3·85	230	4·35
2-Benzyl-4-quinazolone (Glycosminine; III)[1]	312	3·57	303	3·66	—	—	265	3·95	225	4·44
1-Methyl-2-benzyl-4-quinazolone (Arborine; IV)*	315	3·87	306	3·94	277	3·72	268	3·68	227	4·25
3-Methyl-2-benzyl-4-quinazolone (VII)	312	3·61	—	—	272	3·55	269	3·99	227	4·49

* Log ε values calculated from the published curve.[2]

and appearance of a band at 1412 cm^{-1} (7·08 μ) for N–Me corroborates our previous assignments[1] for this class of compound. While the bands at 1676 cm^{-1} (5·97 μ) and around 1585 cm^{-1} (6·31 μ) resolvable in two distinct peaks (not shown in the Fig.) at 1590 cm^{-1} (6·29 μ) and 1580 cm^{-1} (6·33 μ) are characteristic of the quinazolone system, those at 1650 cm^{-1} (6·06 μ) and 1704 cm^{-1} (5·87 μ) may arise from the contribution of the mesomeric forms VIII and IX stabilized by salt formation analogous to glycorine (I) hydrochloride. A strongly bonded ammonium salt character of the hydrochloride is also indicated[1,8] by the triple peaks at 3100 cm^{-1} (3·22 μ), 3060 cm^{-1} (3·27 μ) and 3030 cm^{-1} (3·3 μ) together with the band at 1412 cm^{-1}.



VII R = CH_2Ph VIII IX

Our views[1] that a strong band in the region 1527–66 cm^{-1} (6·55–6·39 μ) is characteristic of only those N-substituted 4-quinazolones which are free from hydrogen bonding and that a band at around 1531 cm^{-1} (6·53 μ) cannot be ascribed to $\rangle C{=}N$ as proposed by Chakravarti *et al.*[2] are further strengthened by the absence of these peaks in the spectrum of VII.

The extreme reluctance of glycosmicine (II) to salt formation precluded its demethylation to the corresponding benzoyleneurea (X). The latter on direct methylation with alkaline methyl iodide is known[7] to yield the 3-methyl-(XI) and then 1,3-dimethyl and not its 1-methyl-(II) derivative. It has also been shown[9] that even during the condensation of N-methylanthranilamide and urea in the preparation of glycosmicine, the Me group migrates from position 1 to 3 to give a mixture of II and XI in 1:1·4 ratio.

Although the position 3 remains the preferred site for methylation in this type of compounds,[6,7] the naturally occurring quinazolones,[10] more often than not, are alkylated in position 1. Furthermore, while one of the lactam forms is least favoured[1,6] by the N-1 unsubstituted 4-quinazolones (V and III), it has been shown[1] to be the preferred one for the corresponding N-1 methyl derivatives (I and IV) irrespective of the substituent at position 2. Therefore, it is believed that according to Robinson's postulate,[11] anthranilic acid, the common biogenetic precursor, gets N-methylated first where necessary and then condenses with ammonia or amine and formic or phenylacetic acid to build up the quinazolone alkaloids as substantiated by their syntheses[1,12] unless the enzymatic reactions should prove to be different. Glycosmicine (II) might arise *via* (i) oxidative fission of arborine (IV) or (ii) from glycorine (I) or dihydroglycorine by oxidation. We subjected arborine to oxidation with chromic acid in acetic acid to ascertain this point and to our surprise both glycosmicine and glycorine, the latter in good yield, could be isolated from the reaction product. However, glycorine under similar condition did not yield any recognizable product. Although this oxidizing agent is already known[7] to oxidize 4-quinazolone (V) to benzoyleneurea (X) apparently through covalent hydration, a phenomenon peculiar to

the quinazoline system,[13] the mechanism of oxidation appears to be different in case of arborine.

We believe that the formation of glycosmicine involves the oxidative cleavage of the benzylidene form of arborine since periodic acid oxidation of the latter reported[14] to yield an uncharacterized product, m.p. 258° proved to be glycosmicine in our hands while glycosminine which does not exist in this form[1] is recovered unchanged. The mechanism of glycorine formation is not yet clearly understood and is being investigated.

EXPERIMENTAL

All m.ps are uncorrected. Brockmann acid washed alumina was used throughout unless otherwise stated. R_f values refer to TLC run on silica gel G of layer thickness 0·2 mm in solvent system EtOAc: HCOOH: $CHCl_3$: MeOH (40:30:25:5), plates dried at 120° for 30 min and sprayed with I_2 soln. Analyses are by Dr. Alfred Bernhardt, Max Plank Institüt, Mülheim, W. Germany.

Conversion of glycorine (I) *to 4-quinazolone* (V). Glycorine hydrochloride (0·2 g) was sublimed at 250° under vacuum (8–10 mm). The sublimate (0·15 g) on crystallization from water yielded (20%) needles, m.p. 218–220°. It was then converted to its hydrochloride by treatment with a few drops of conc HCl in abs EtOH yielding white needles m.p. 272–273°. The base was identified as 4-quinazolone by direct comparison (m.m.p., IR) with a synthetic specimen, R_f value 0·46.

N-methylation of 4-quinazolone (V) *to 3-methyl derivative* (VI)

(a) The method analogous to that of Pachter *et al.*[4] was followed. A soln (40 ml) of 4-quinazolone (0·6 g) in abs. EtOH was added to a refluxing soln of Na (0·15 g) in the same solvent (60 ml). MeI (0·5 ml) in alcohol (2 ml) was added followed by some more Na (0·15 g). The alternate addition of alc. MeI and Na in the same amounts was repeated 6 times and the mixture was refluxed for 2 hr.

The reaction product was then cooled, poured on to ice-cold water (200 ml) and extracted with $CHCl_3$. The extract was then washed free from alkali, dried (Na_2SO_4) and evaporated. The gummy residue (0·3 g) was crystallized several times from benzene–pet ether in transparent needles, m.p. 105°; picrate, m.p. 215°. (Found: C, 46·48; H, 3·15; N, 17·53. Calc. for $C_9H_8N_2O$. $C_6H_3N_3O_7$: C, 46·27; H, 2·85; N, 17·99%.) The physical constants are in agreement with those reported[15] for 3-methyl-4-quinazolone, R_f value 0·48.

(b) 4-Quinazolone (1 g) dissolved in 99–100% formic acid (4 ml) was treated with 40% formaldehyde (10 ml) and the mixture was heated on water-bath. After 4 hr, HCHO (10 ml) was again added to it and the heating continued for additional 4 hr. The mixture was then poured on to ice-cold water (200 ml), basified (Na_2CO_3) and extracted with $CHCl_3$, washed, dried and concentrated. The residue (0·8 g) was chromatographed over a column (25 × 1 cm) of alumina. The fractions eluted with benzene (150 ml) upon evaporation and crystallizations from benzene–pet. ether yielded 3-methyl-4-quinazolone (0·05 g), m.p. 104–105° already prepared. Further elution with $CHCl_3$ recovered unchanged starting material.

Conversion of arborine (IV) *to glycosminine* (III). Arborine hydrochloride (0·1 g) was heated at 250° in an oil-bath under vacuum (10–12 mm) in a sublimation tube. The residual mass was then crystallized twice from alcohol (20 mg) in needles, m.p. 248–249°. Its identity with glycosminine was established by the superimposable IR spectrum of an authentic specimen, R_f value 0·57.

N-methylation of glycosminine to its 3-methyl derivative (VII) *and arborine* (IV)

Glycosminine (0·2 g) dissolved in abs. EtOH (20 ml) was added to a refluxing soln of Na (0·05 g) in the same solvent (20 ml) followed by MeI (0·15 ml) in EtOH (0·6 ml). The crude reaction mixture (0·14 g) obtained by the procedure already described was resolved by chromatography over a column (8 × 1 cm) of alumina into the following fractions:

The benzene eluate (200 ml) on concentration yielded a white sticky substance (0·1 g), m.p. 95° which could not be induced to crystallize, R_f value 0·55. It formed crystalline picrate, m.p. 179° (dec), picrolonate, m.p. 182° and hydrochloride, m.p. 224° (dec). (Found: C, 54·93; H, 3·41; N, 15·10. $C_{16}H_{14}N_2O$, $C_6H_3N_3O_7$ requires: C, 55·11; H, 3·55; N, 14·61%.)

While 30% $CHCl_3$ in benzene (120 ml) recovered unchanged glycosminine (10 mg), m.p. 249° further elution with 80% $CHCl_3$ in benzene (50 ml) afforded arborine (0·015 g), m.p. 154–155° R_f values 0·41, 0·42; picrate, m.p. 173–174° (dec), the identity of which was established by m.m.p. and IR with authentic samples.

Glycorine (I) *and glycosmicine* (II) *from arborine* (IV). A soln of arborine (0·5 g) in minimum amount of AcOH was heated with CrO_3 (0·9 g) in AcOH for 30 min on water-bath. The reaction mixture was cooled and without further dilution basified with NH_4OH. The base separated as a viscous mass was extracted with CH_2Cl_2 and worked up as usual.

The total base (0·32 g) was dissolved in C_6H_6 containing a few drops of CH_2Cl_2 and chromatographed over alumina column (8 × 1·2 cm). Elution with 40% CH_2Cl_2 in C_6H_6 (300 ml) afforded a crude solid (0·05 g) which on crystallization from CH_2Cl_2–MeOH proved to be identical with glycosmicine, m.p. 272° in all respects, R_f value 0·56.

Further elution with 60% CH_2Cl_2 (175 ml) yielded a viscous oil (0·25 g) that was rechromatographed on a column (14 × 1·2 cm) of alumina. Elution with 1% MeOH in CH_2Cl_2 again furnished an oil (0·2 g) which from benzene soln deposited long colourless needles but could not be isolated as such due to its hygroscopic nature reminescent of the behaviour of glycorine. The base however formed well defined, stable hydrochloride, m.p. 242° (dec) and a picrate, m.p. 249° (dec). The regenerated base on crystallization and drying immediately following rapid filtration melted at 145–147°. It was identical in all respects with an authentic sample of glycorine isolated in our laboratory, R_f values 0·24, 0·25.

Periodic acid oxidation of arborine (IV) and glycosminine (III). A soln of 0·2N HIO_4 (50 ml) was added to a soln of arborine hydrochloride (0·2 g) in water (50 ml) and the mixture was left aside for 4 hr. It was then steam distilled and the distillate (200 ml) was extracted with $CHCl_3$. The organic layer yielded benzaldehyde, characterized through its 2,4-DNP derivative, m.p. 235°. The pH of the aqueous layer was adjusted to 10–11 (Na_2CO_3) and the liberated base was extracted with $CHCl_3$. The usual work up gave a residue (0·06 g) which proved to be glycosmicine,[1] m.p 269–270° on recrystallizations twice from alcohol.

Glycosminine hydrochloride which was practically insoluble in water remained unaffected by similar treatment and the original base was recovered.

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