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STUDIES ON INDIAN MEDICINAL PLANTS—VI*

STRUCTURES OF GLYCOSMICINE, GLYCORINE AND GLYCOSMININE, THE MINOR ALKALOIDS FROM *GLYCOSMIS ARBOREA* (ROXB.) DC†

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Abstract—On the basis of physical methods, three minor alkaloids from *Glycosmis arborea* (Roxb.) DC., *viz.* glycosmicine, glycorine and glycosminine have been assigned the following structures: 1-methyl-2-keto-1,2-dihydro-4-quinazolone (II), 1-methyl-4-quinazolone (V) and 2-benzyl-4-quinazolone (XIII), respectively. It has been observed that the alkaloids exist in equilibrium forms. The structures have been confirmed by synthesis in each case. The mass spectra and the infra-red spectral characteristics of the quinazolone derivatives have been discussed in detail.

IN A preliminary communication,[1] we reported the isolation of three minor alkaloids, *viz.* glycosmicine, m.p. 270–271°, glycorine, B.HCl, m.p. 242°, and glycosmine, m.p. 249° from the leaves of *Glycosmis arborea* (Roxb.) DC. (*Rutaceae*). Meanwhile, it has been possible to establish[2] the identity of the last named alkaloid with glycosminine, m.p. 225–227°, earlier reported by Chatterjee and Ghosh Majumdar[3] from *G. pentaphylla.* However, Chakravarti *et al.*[4] have already pointed out and we have good reason[2] to believe that the species involved is *arborea* and not *pentaphylla.*

Although glycosminine was definitely not isolated in the pure form (only the melting point was recorded in the literature[3] prior to our work) yet the name has precedence and hence we abandon the use of the name 'glycosmine'.

While glycosminine was isolated from the basic portion of the petroleum ether extract of the leaves (after separation of arborinine), glycorine and glycosmicine together with other constituents were obtained from the subsequent benzene extract by chromatography. Details of the extraction procedure will shortly appear elsewhere.[2] This paper reports the complete structural elucidation of the three alkaloids without

* For part V of this series *see* ref. 2.

† A short account of the work contained herein has been presented by one of us (S. C. P.) at the *2nd International Symposium on the Chemistry of Natural Products*, Prague, Aug. 27–Sept. 2, 1962.

[1] S. C. Pakrashi and J. Bhattacharyya, *J. Sci. Industr. Res.* (*India*), **21B**, 49 (1962).
[2] S. C. Pakrashi and J. Bhattacharyya, *Ann. Biochem. Exptl. Med.* (*India*), **23**, 123 (1963).
[3] A. Chatterjee and S. Ghosh Majumdar, *J. Amer. Chem. Soc.*, **76**, 2459 (1954).
[4] D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Das Gupta, S. Datta and H. K. Miller, *Tetrahedron*, **16**, 224 (1961).

recourse to classical degradations thus establishing the value of modern physical methods in constitutional studies.

Glycosmicine

Glycosmicine, m.p. 270–271°, analyses for $C_9H_8N_2O_2$ and has only one active hydrogen. The result of $—OCH_3$ or $N—CH_3$ estimation was so low that normally the presence would have been excluded.

The U.V. absorption spectra in ethanol with maxima at 219 (log ϵ 4·70), 244 (log ϵ 3·97) and 311 (log ϵ 3·64) mμ remain practically unaltered in 0·01N HCl, but in 0·01N NaOH, the high intensity band at 244 mμ disappears and the maxima

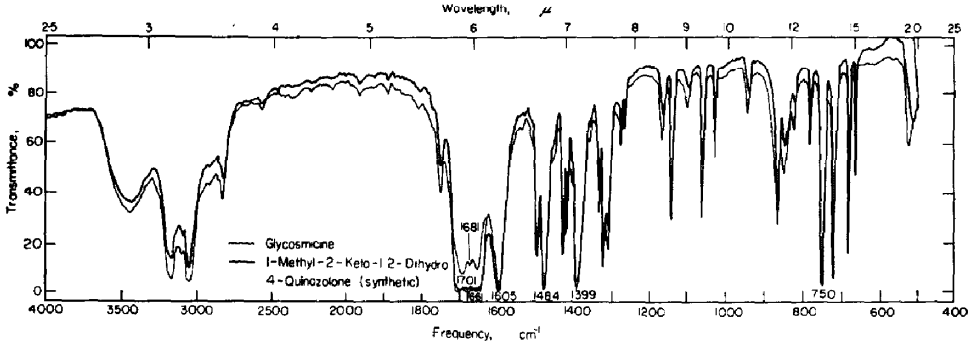


FIG. 1. Infra-red spectra of glycosmicine (natural and synthetic) in KBr.

appears at 223 (log ϵ 4·70) and 313 (log ϵ 3·75) mμ. This spectral characteristic is characteristic of a diketo compound (cf. benzoyl acetone[5]) capable of existing in keto-enol forms and indicates the possibility of a 2,4-quinazolinedione structure for glycosmicine.

This is supported by the I.R. spectrum of the compound (Fig. 1) in KBr which exhibits among others two strong peaks at 1701 cm^{-1} (5·88 μ) and 1661 cm^{-1} (6·02 μ) corresponding to two carbonyl functions, one at 4- and the other at 2-positions[6a] along with two bands at 1605 cm^{-1} (6·23 μ) and 1484 cm^{-1} (6·74 μ) typical for a quinazolinedione system.[7] The band at 1399 cm^{-1} (7·15 μ) is assigned to $N—CH_3$.

Initially, the N.M.R. spectrum* (Fig. 2) of a saturated solution (< 5 mg in 0·5 ml) in $CDCl_3$ was studied. The largest line at 215 cps ($\delta = 3·58$) could be assigned to either a $—OCH_3$ or $N—CH_3$ group. The sets of signals around the chloroform peak are from four protons all on the same benzene ring; that one must be *peri* to a carbonyl group is indicated by the doublet signal at 493 cps ($\delta = 8·22$). The triplet signal (463 cps; $\delta = 7·72$) just to the right of this and two peaks (441, 428 cps) flanking that of the chloroform must be assigned to three more protons in the said ring. The broad signal at 515 cps ($\delta = 8·59$) should be assignable to a hydrogen bonded NH.

* Run in all cases in Varian spectrometer with tetramethyl silane as internal standard and unless specifically mentioned otherwise in a 60 mc instrument.

$$\delta = [(H_{SiMe_4} - H)/H_{SiMe_4}]/10^6 = \text{p.p.m. downfield from } SiMe_4.$$

[5] A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry* (2nd ed.), p. 262. Edward Arnold, London (1957).

[6] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (1st ed.), (a) pp. 190–207, (b) p. 285. John Wiley, New York (1956).

[7] H. Culbertson, J. C. Decius and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 4834 (1952).

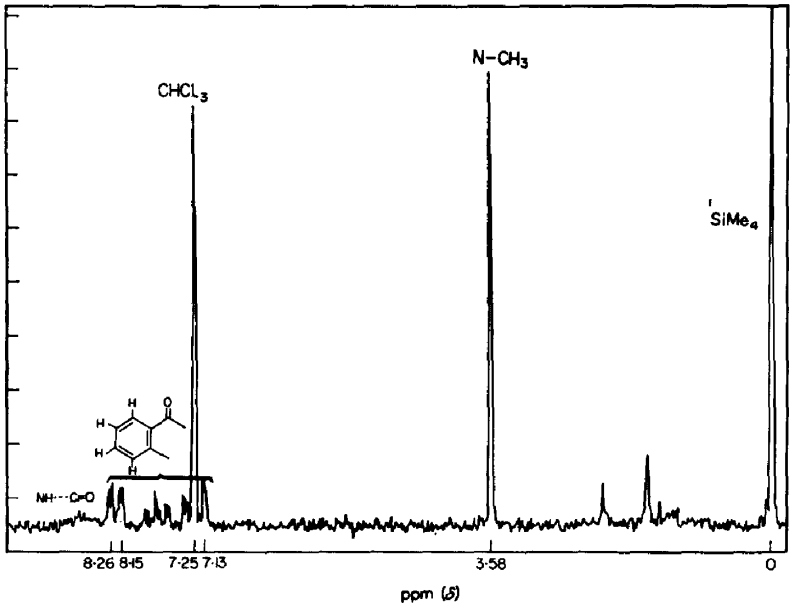


FIG. 2. Nuclear magnetic resonance spectrum of glycosmicine in $CDCl_3$.

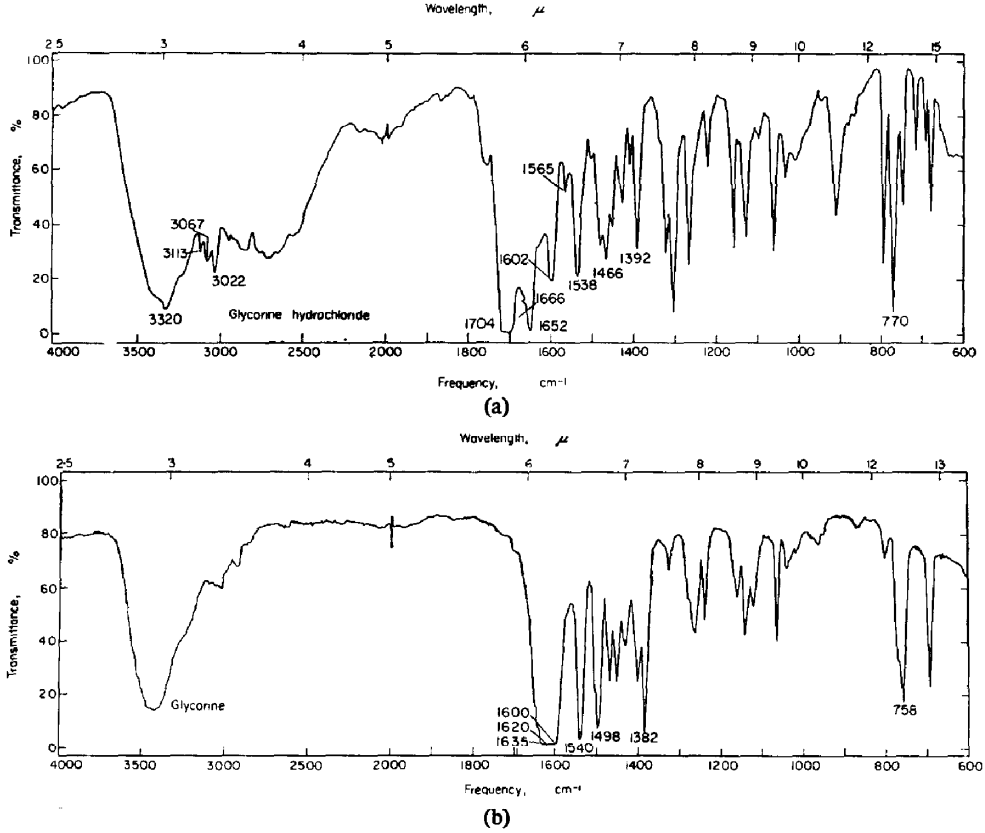
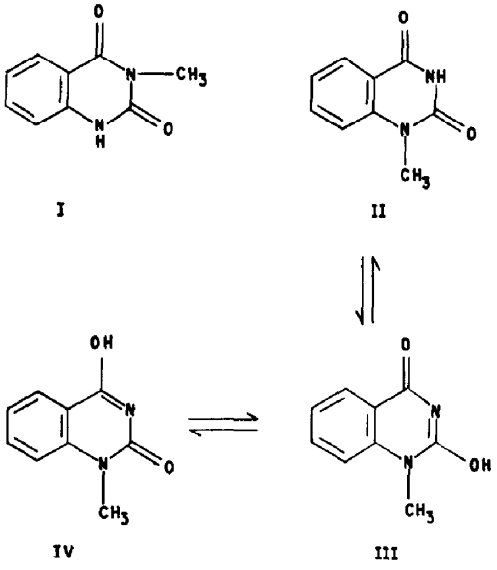


FIG. 3. Infra-red spectra of glycorine hydrochloride (a) and glycorine (b) in KBr.

Thus the eight protons are accounted for. The peaks at 96 cps and 130 cps may be due to the trace of water in the sample and a very small amount of acetone in the solvent.

The foregoing data may be accommodated only in the expressions I and II.



Structure I represents a known compound with reported[8] m.p. 234° and therefore glycosmicine must have structure II which was confirmed by direct comparison with a synthetic sample* of 1-methyl-2-keto-1,2-dihydro-4-quinazolone, the mixture melting point being undepressed, and the U.V. and I.R. (Fig. 1) absorption spectra identical in all respects. Although the synthetic compound has been known for a long time,[8] this is the first report of its occurrence in nature.

Possibly, II may not be the exclusive structure for glycosmicine, the high melting point, insolubility in dilute acids† and in most organic solvents may be explained[9], like benzoyleneurea, by assuming the existence of tautomeric forms II–IV with the predominance of the diketo form II even in the solid state. The U.V. shift in the alkaline medium tends to support this view although structure IV would be incompatible with the N.M.R. data.

Glycorine

It is a tertiary, hygroscopic base which could not be isolated crystalline in the free state although in solution it is deposited in long colourless needles. It could however be purified through its stable salts, *inter alia*, hydrochloride, m.p. 242° (dec) or picrate, m.p. 249° (dec). The regenerated base on crystallization and immediate

* We are grateful to Prof. (Mrs.) A. Chatterjee[8] for the kind supply of the sample.

† The reported[1] B.HCl, m.p. 272°, turned out to be the purer variety of the base itself which remained unaffected by concentrated hydrochloric acid.

[8] C. H. Wang and B. E. Christensen, *J. Amer. Chem. Soc.*, **71**, 1440 (1949) and the references cited therein.

[9] T. A. Williamson in R. C. Elderfield, *Heterocyclic Compounds*, Vol. VI, pp. 327, 352, John Wiley, New York (1957).

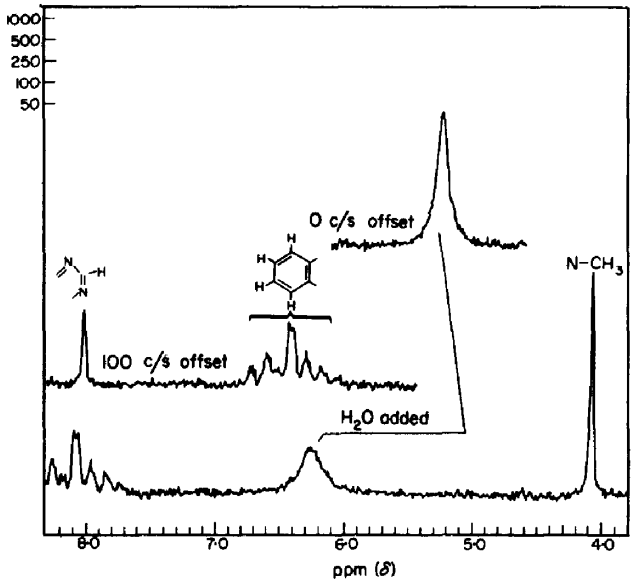


FIG. 4. Nuclear magnetic resonance spectrum of glycorine hydrochloride in dimethyl sulphoxide.

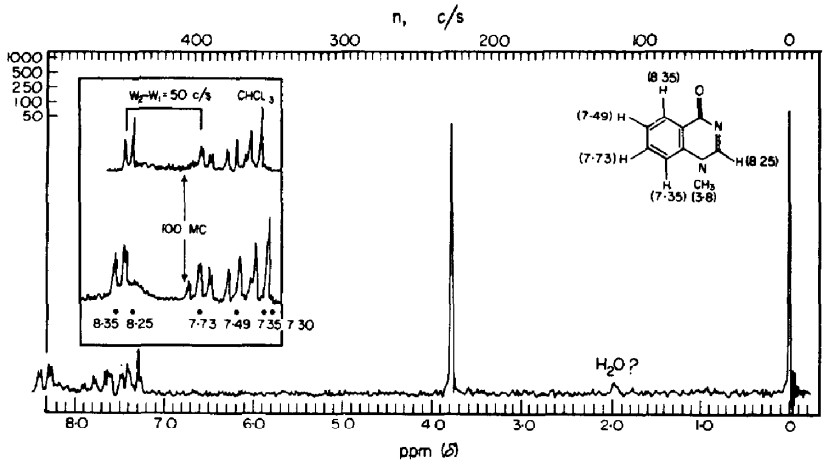


FIG. 5. Nuclear magnetic resonance spectrum (60 mc) of glycorine in dimethyl sulphoxide with proton spin-spin decoupling spectrum inset.

drying melted at 145–147°. On the basis of the analyses of its salts, the molecular formula of the base, $C_9H_8N_2O$, is corroborated by mass spectroscopy, the *m/e* 160 peak corresponding to the molecular ion. It contains one N—CH_3 but no —OCH_3 or active hydrogen.

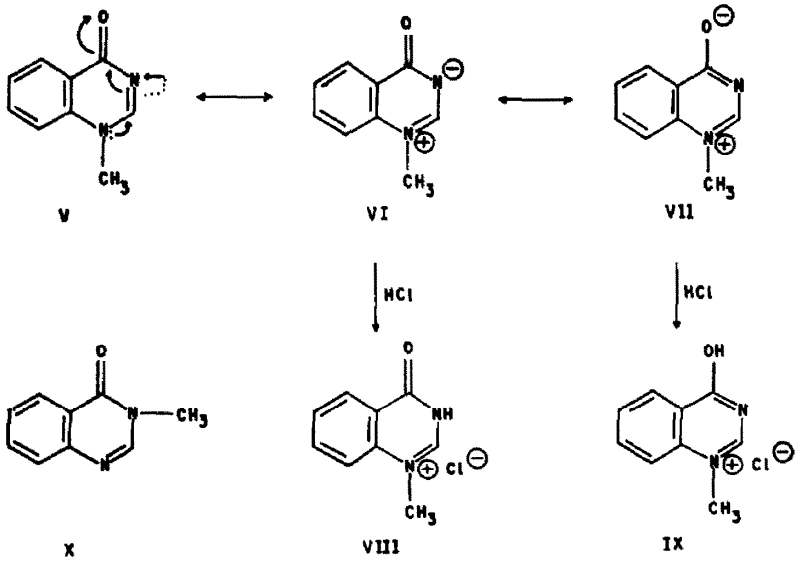
The U.V. absorption spectrum of the base in ethanol shows λ_{max} at 269 (log ϵ 3·59), 278 (log ϵ 3·66), 306 (log ϵ 3·91) and 317 (log ϵ 3·84) mμ; the values being practically the same as reported for 1-methyl-4-quinazolone.[10] In 0·01 N HCl, the maxima shifts to 282 (log ϵ 3·68), 295 (log ϵ 3·73) and 304 (log ϵ 3·69) mμ.

The I.R. spectrum (Fig. 3a) of the base hydrochloride in KBr pellets shows triplet

[10] J. M. Hearn, R. A. Morton and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951).

bands at 3113 (3·21 μ), 3067 (3·26 μ) and 3022 (3·31 μ) cm^{-1} coupled with the strong band at 1392 cm^{-1} (7·18 μ) indicative of the strongly bonded ammonium salt character of the compound (cf. ammonium nitrate[11]). The 3320 cm^{-1} (3·01 μ) band may possibly be assigned to the solvent of crystallization rather than the NH stretching frequency in such compounds.[4] As, only NH with least or no hydrogen bonding could be expected to absorb in this region (cf., ammonium perchlorate) and contrary to the fact, the compound would be incapable of absorbing water.[6b] The bands at 1704 cm^{-1} (5·87 μ), 1652 cm^{-1} (6·05 μ), the split peak at 1602 cm^{-1} (6·24 μ) and perhaps the band[4] at 1538 cm^{-1} (6·50 μ) may be adduced to the 4-quinazolone system.[7] The peak at 1652 cm^{-1} would also be expected[6a] of a pyridyl betaine type of compound. The other bands have their usual significance.

It may be observed in the I.R. spectrum (Fig. 3(b)) of the free base in KBr that the acyl carbonyl absorbs at a frequency (1635 cm^{-1}) 69 cm^{-1} lower than that of the hydrochloride which should, according to Culbertson *et al.*[7], be attributed to the direct conjugation of the carbonyl with a —N=C< function. The large shift of the same frequency in the hydrochloride may thus be explained by assuming that the base (V) changes into its possible zwitter ionic forms VI and VII and the latter are stabilized by salt formation. The I.R., therefore, strongly suggests structures VIII or IX for the hydrochloride, the former being preferable to explain the N-acyl carbonyl band at 1704 cm^{-1}.



The N.M.R. spectrum of glycorine hydrochloride (Fig. 4) in dimethyl sulphoxide supports the presence of eight protons in a quinazoline framework. The signals centered around 485 cps ($\delta = 8{\cdot}08$) are due to four benzene-ring protons. The low-field shift of these signals suggests two fused aromatic rings.

The structure IX rather than the more usual ketonic form VIII for the hydrochloride is indicated by N.M.R. and supported by the following observations: On the basis of the keto-isomer, the proton on the carbon between two nitrogens would no longer

[11] F. A. Miller and C. H. Wilkins, *Anal. Chem.* **24**, 1253 (1952).

be on the aromatic ring and would not be expected to be seen quite so far downfield as 581 cps ($\delta = 9{\cdot}68$). Also the appearance of N—CH_3 peak observed at 245 cps ($\delta = 4{\cdot}08$) rather than the more normal shift of 230 cps ($\delta = 3{\cdot}83$) can be accounted for by assuming pyridyl type methyl group.

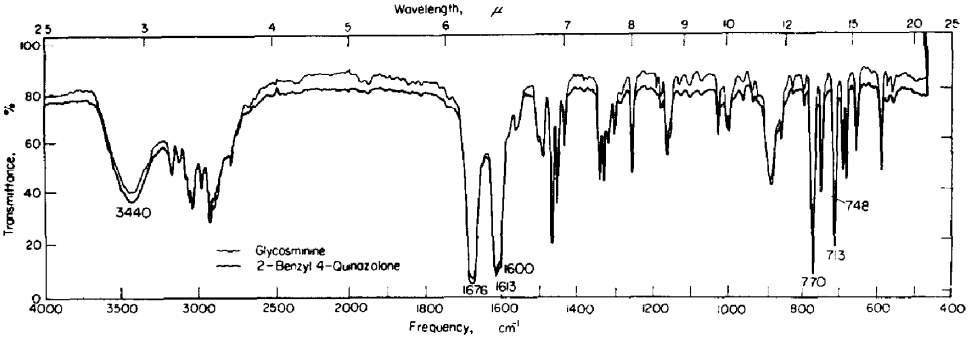


FIG. 6. Infra-red spectra of glycosminine (natural and synthetic) in KBr.

The peak at 375 cps ($\delta = 6{\cdot}25$) is assigned to water. The integrals of three other sets of signals amounts exactly to four protons suggesting a dihydrate. To verify this assignment, a trace of water was added to the solution and this signal grew and shifted towards higher field. However, the duplicate analysis obtained for the hydrochloride is compatible only with 2/3 H_2O of crystallization. Therefore, it is suggested that in the molecule (IX) the 'OH' proton is exchanging with the water of hydration to produce a single broad peak observed in the spectra. The base could then be represented by either V or VII. The possibility of glycorine being 3-methyl-4-quinazolone (X) was eliminated because the latter in the anhydrous state has a reported[12] m.p. 105° the picrate[13] of which melts at 215–216°. On the other hand, Morley and Simpson[13] and Leonard and Ruyle[14] who synthesized it by other methods report 1-methyl-4-quinazolone (V) to have characteristics similar to glycorine. The base was also synthesized by condensing N-methyl-anthranilamide with ethyl orthoformate, and this synthetic sample is identical in all respects with an authentic specimen of 1-methyl-4-quinazolone* which in turn is identical with the natural product by mixed melting point, I.R. and N.M.R. comparisons.

It may be noted that the 100 mc N.M.R. spectrum (Fig. 5) of 1-methyl-4-quinazolone in dimethyl sulphoxide is far more simple for actually assigning chemical shifts to the four benzene ring protons. In addition, information from proton spin–spin decoupling verified that the proton the triplet signal of which is centered around $\delta = 7{\cdot}73$ is spin coupled to the proton directly across the carbonyl group with a spin coupling constant of about 2 cps producing the smaller splitting in the group of signals centered around $\delta = 8{\cdot}35$. Since the smaller splitting is characteristic of a *meta* spin–spin coupling, we can assign the triplet at $\delta = 7{\cdot}73$ to the proton which is *meta* to the proton *peri* to the carbonyl. Two other ring protons are assigned on

* We are indebted to Prof. R. A. Morton of the University of Liverpool, U.K., for kindly making this sample available to us.

[12] M. T. Bogert and G. A. Geiger, *J. Amer. Chem. Soc.*, **34**, 683 (1912).
[13] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1354 (1949).
[14] N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, **13**, 903 (1948).

the basis of the relative intensities of the signals in the light of the spin coupling between them and their small, relative chemical shift. The base glycorine must, therefore, predominantly exist in the stabler form V.

Glycosminine

It has a molecular formula, $C_{15}H_{12}NO_2$, contains one active hydrogen and no N—CH_3 or —OCH_3 groups. The U.V. spectrum in ethanol shows λ_{max} at 225 (log ϵ 4·44), 265 (log ϵ 3·95), 303 (log ϵ 3·66) and 312 (log ϵ 3·57) mμ. The values are close to those reported[10] for 4-hydroxy-quinazoline or 3-methyl- than for 1-methyl-4-quinazolone.

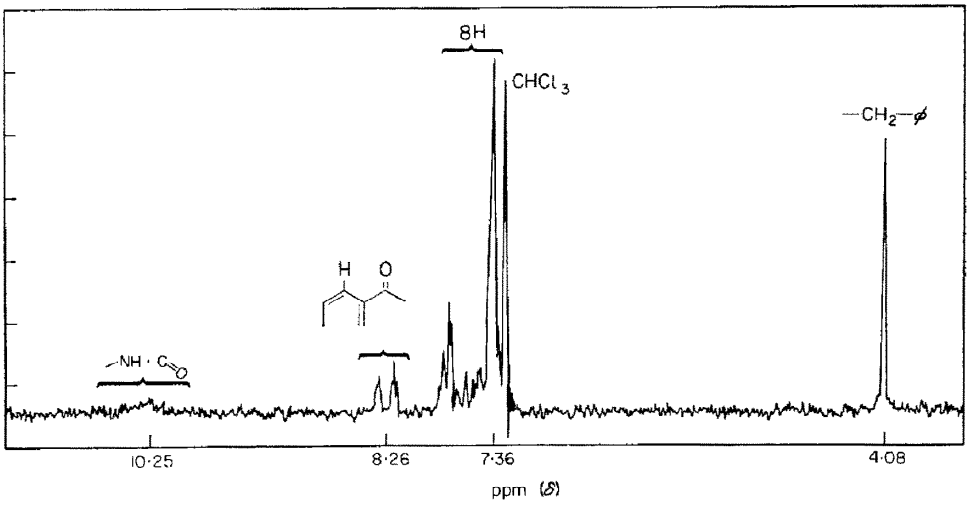


FIG. 7. Nuclear magnetic resonance spectrum of glycosminine in $CDCl_3$.

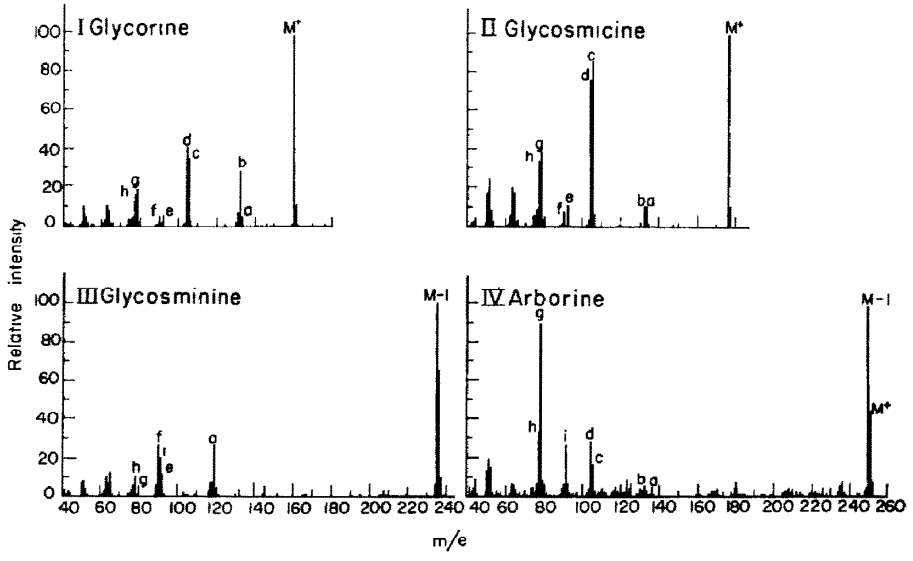
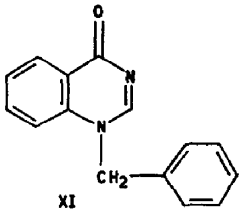


FIG. 8. Mass spectra of glycorine, glycosmicine, glycosminine and arborine.

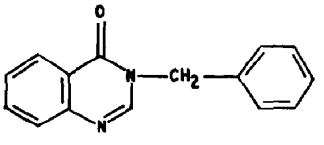
The I.R. spectrum of glycosminine is reproduced in Fig. 6. Although the broad band at 3440 cm^{-1} (2·90 μ) may have been due to the moisture present in the KBr used (control spectrum not shown in the Fig.) in another run, a sharper band at 3356 cm^{-1} (2·98 μ) indicates the presence of either a NH or OH group in the molecule. The band at 1676 cm^{-1} (5·97 μ) and 1613 cm^{-1} (6·20 μ) would suggest the structure 2- or 3- (or both) substituted 4-quinazolone rather than its 1,2-substituted analogue (Table 1). The strongest peak at 770 cm^{-1} (12·98 μ) must be due to *o*-disubstitution and the medium band at 748 cm^{-1} (13·37 μ) together with another strong band at 713 cm^{-1} (14·03 μ) could be assigned to a monosubstituted benzene ring in the system.

The N.M.R. spectrum (Fig. 7) of a supersaturated solution of the compound in $CDCl_3$ supports the total proton count. The signal at the lowest field, 615 cps ($\delta = 10{\cdot}25$), is typical of a hydrogen bonded NH. The doublet peak at 496 cps ($\delta = 8{\cdot}26$) is characteristic of a hydrogen on a benzene ring *peri* to the carbonyl. The signal at 245 cps ($\delta = 4{\cdot}08$) has an area equivalent to two hydrogens and must be from a $—CH_2—$ group directly attached to a benzene ring and one other deshielding group (such as nitrogen). The large group of signals around 450 cps ($\delta = 7{\cdot}5$) are accountable to the remaining hydrogens.

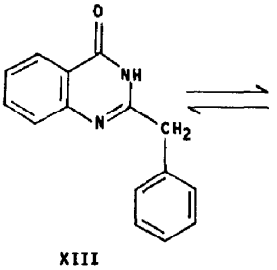
These data suggest structural possibilities XI–XIII for glycosminine, and the formula XIV was also taken into consideration in view of its co-occurrence with arborine (XVI).[4]



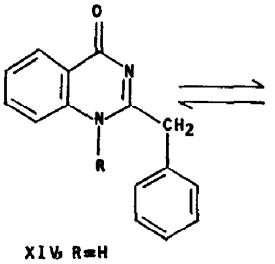
XI



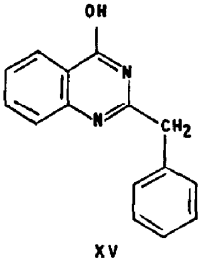
XII



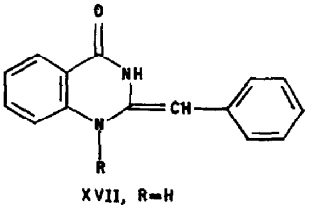
XIII



XIV, R=H
XVI, R=CH_3



XV



XVII, R=H
XVIII, R=CH_3

TABLE 1. INFRARED ABSORPTION* AT 1400–1704 cm^{-1} (7·15 – 5·87 μ) REGION FOR SOME QUINAZOLONE DERIVATIVES

No.	Name of the Compound	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$
1.	2-Quinazolone[7]	1684 1645	5·94 6·08	1608	6·22	—	—	1500	6·67	—	—	1417	7·05
2.	4-Quinazolone[7]	1704 1664	5·87 6·01	1608	6·22	—	—	—	—	—	—	—	—
3.	2-Methyl-4-quinazolone[7]	1676	5·97	1625	6·15	—	—	—	—	1478	6·76	1421	7·04
4.	3-Methyl-4-quinazolone[7]	1676	5·97	1612	6·20	1557	6·42	—	—	1473	6·79	1439	6·95
5.	2,3-Dimethyl-4-quinazolone[7]	1672	5·98	1593	6·28	1566	6·39	—	—	1466	6·82	1415	7·07
6.	1,2-Dimethyl-4-quinazolone[7]	1637	6·11	1597	6·26	1534	6·52	1498	6·68	—	—	1406	7·11
7.	1,2-Dimethyl-4-quinazolone[4]	1642	6·09	1608	6·22	1534	6·52	1504	6·65	1453	6·88	1431	6·99
8.	2-Ethyl-1-methyl-4-quinazolone[4]	1626	6·15	1608	6·22	1527	6·55	1493	6·70	1458	6·86	1441	6·94
9.	Arborine[4] (1-Methyl-2-benzyl-4-quinazolone)	1645	6·08	1603	6·24	1531	6·53	1502	6·66	1456	6·87	—	—

TABLE 1 (*continued*)

No.	Name of the Compound	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$	ν cm^{-1}	$\lambda_{max}(\mu)$
10.	Glycosminine (2-Benzyl-4-quinazolone	1676	5·97	1613 1600 sh	6·20 6·25	—	—	1485	6·74	1461	6·84	1448 1429	6·91 7·00
11.	Glycorine Hydrochloride	1704 1666 sh 1652	5·87 6·00 6·05	1602 1598 (split peak)	6·24 6·26	1538	6·50	1480 sh	6·76	1466	6·82	1450 1428	6·89 7·01
12.	1-Methyl-4-quinazolone (Glycorine)	1635 1620	6·12 6·17	1600	6·25	1540	6·49	1498	6·68	1470 1452	6·80 6·89	1430	7·00
13.	Dihydroarborine[4]	1653	6·05	1605	6·23	—	—	1497	6·68	1451	6·89	1435	6·97
14.	2,3-Dihydro-1,2-dimethyl-4-quinazolone[4]	1658	6·03	1610	6·21	—	—	1493	6·70	—	—	1447 ~1441	6·91 6·94
15.	2,3-Dihydro-2-ethyl-1-methyl-4-quinazolone[4]	1658	6·03	1610	6·21	—	—	1497	6·68	—	—	—	—
16.	Glycosmicine(1-methyl-2-keto-1,2-dihydro-4-quinazolone)	1701 1684 1661	5·88 5·95 6·02	1605	6·23	—	—	1484	6·74	—	—	1433 1422	6·98 7·03

* The spectra of nos. 1, 2, 5 and 6 have been studied in Nujol mull, 3, 4 as melt and the rest in KBr pellets.

The structures XI and XII can neither explain the presence of an NH group nor an active hydrogen and the U.V. spectrum of the former should be different.[10]

Structure XIII is more likely to represent glycosminine than XIV because of the downfield shift of the NH peak in N.M.R. (due to the hydrogen bonding with the carbonyl group).

Finally, the structure was proved by synthesis from anthranilamide[15] and phenylacetyl chloride[4] or phenylacetic acid.[16]* The synthetic sample is identical with the natural product by mixed melting point and I.R. comparison (Fig. 6). The synthetic sample cannot, however, distinguish between the isomeric structures XIII and XIV.

Unless substitution by a benzyl group at 2-position would otherwise influence the relative abundance of the tautomeric forms and having the same maxima and proportionate molecular extinction values in the U.V., glycosminine may reasonably be expected to exist, like 4-hydroxy-quinazoline, in all the possible tautomeric forms XIII–XV with the preponderance of the keto dihydro form XIII which has been shown[10] to exist in by far the largest proportion in 4-hydroxy-quinazoline, quinoline and cinnoline. However, the possibility of XV may be ruled out on the basis of physical methods already discussed.

Arborine, the only other quinazoline alkaloid from *G. arborea* besides those isolated by us has recently been shown[4] to have the structure XVI in preference to XVIII proposed by Chatterjee and Ghosh Majumdar.[3] The N.M.R. evidence is more convincing in establishing the correct structure. In connection with this work, we have examined arborine in a 60 mc instrument and came to the same conclusion. We have already shown that glycosminine having the preferred structure XIII shows a signal at 615 cps ($\delta = 10{\cdot}25$) typical of a hydrogen bonded NH. This could then also be expected of the structure XVIII. However, the spectrum of arborine in addition to what has already been reported by Chakravarti *et al.*[4] shows no signal in this region which is of course to be expected since the area of the signal at 204 cps ($\delta = 3{\cdot}40$) is just 2/3rd of that from the methyl signal at 219 cps ($\delta = 3{\cdot}65$). Since a tautomeric form can only exist at the expense of the —CH_2— signals this indicates that there are no such forms present which could convert the —CH_2— protons to an olefinic and NH protons.

As mass spectrometric studies[17] have proved of immense value in the structural determinations of alkaloids, the study was extended to the 4-quinazolone bases from *G. arborea*. The spectra reproduced in Fig. 8 not only support the established structures discussed but also yield valuable information regarding the fragmentation pattern of this class of alkaloids.

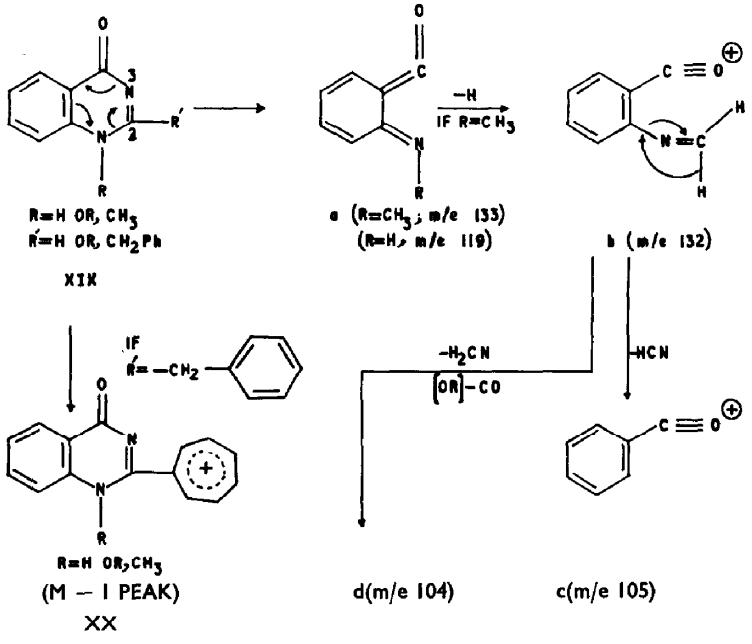
* After we completed the synthesis with phenylacetyl chloride, our attention was drawn to a report (S. K. Roy, S. Ghosh Majumdar and A. Chatterjee, *Proc. 47th Indian Sci. Cong.*, Part III, 145 (1960) that anthranilamides irrespective of the substitution at N_1 *always* yield the 2-benzylidene-4-quinazolones when reacted with phenylacetic acid. Under similar reaction condition, we however obtained glycosminine as the sole product which is definitely 2-benzyl- rather than 2-benzylidene-4-quinazolone (XVII). The latter is ruled out because it requires two instead of one active hydrogen actually present in glycosminine. Besides, the N.M.R. shows a single sharp NH proton peak and no characteristic signal of an olefinic proton appears in the region of 245 cps ($\delta = 4{\cdot}08$).

[15] R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **13**, 347 (1948).

[16] A. Chatterjee and S. Ghosh Majumdar, *J. Amer. Chem. Soc.*, **75**, 4365 (1953).

[17] L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 2161 (1962) and the references cited therein.

In general, the first fragmentation step of the quinazolone alkaloids seems to be the loss of the atoms 2 and 3 together with their substituents by concerted cleavage (arrows in XIX) leading to species *a*. This transition could be verified by the presence of metastable ions in glycorine at *m/e* 110 (calc. for 160 → 133 110·5) and glycosmicine at *m/e* 101 (calc. for 170 → 133 100·5). In the case of R = CH_3 in *a*, further loss of one hydrogen may lead to structure *b*. The N-methyl group is probably involved in this transformation and this is strongly suggested by the fact that only those compounds containing such grouping, viz. glycorine, glycosmicine and arborine exhibit a peak corresponding to *b* even in greater intensity than *a*. Although in glycorine *m/e* 132 (assigned to species *b*) may in part be derived by loss of CO from a molecular ion, a feature that has been encountered both with aromatic ketones and phenols, this type of fragmentation does not appear likely in the case of glycorine since M − 28 peaks are practically absent in all the other spectra.



The presence of metastable ions in the spectra of glycosmicine and glycorine at *m/e* 83·5 (calc. for 132 → 105 82·5) seems to indicate that the next fragmentation step starts from ion *b* involving the loss of 27 mass units. Since both substituents in *b* (CO and —N=CH_2) amount to the mass 28, it is difficult to ascertain which one is lost (accompanied by rearrangement of one H) in this step not having available a high resolution spectrum. However, as the breaking down fragment appears to be species *b* (as shown by the presence of the metastable ion) the formation of the ion *m/e* 105 (*c*) by a loss of 27 mass units may well be accounted for by assuming a loss of HCN (indicated in *b*) since both the neutral fragment and the resulting ion would be well stabilized. The virtual absence of the fragment *c* (*m/e* 105) in the spectrum of glycosminine, is not, however, surprising since the loss of NH fragment from *a* (R = H) would be energetically a very unfavoured process.

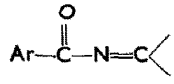
The formation of *d* (*m/e* 104) may be explained either by the loss of H_2CN or more probably, of a molecule of CO from *b*. Fragment *d* in the case of glycosminine represents C_6H_4N moiety and its mass therefore shifts to *m/e* 90, its genesis could be loss of the elements of CHO from species *a* (R = H).

The ions *e* and *f* (*m/e* 92 and 90) may represent C_6N-fragments but it does not lead us very far to speculate on their possible structures. The two peaks *m/e* 78 (*g*) and *m/e* 77 (*h*) correspond to benzene and phenyl respectively. A metastable peak at *m/e* 57, both in the spectra of glycosmicine and glycorine does not allow an unequivocal assignment to either the transition 105 → 78 or 104 → 77. Both ions represent stable species although the formation of benzene is somewhat unexpected. The strong *m/e* 78 peaks (especially in arborine) might as well be due to retained benzene of crystallization, rather than genuine fragmentation.

It is very important to note that the very strong M − 1 peaks exhibited by glycosminine and arborine both of which contain a benzyl substituent should be related to the presence of this function. It is well-known that such a group easily splits off either a substituent or hydrogen and rearranges to highly stabilized tropylium ions, corresponding peak (*i*) at *m/e* 91 (C_7H_7) shown by both the alkaloids strongly supports the above view. It seems reasonable, therefore, to assign the peaks at M − 1 to structure XX.

As more alkaloids with a quinazolone framework are known, the IR characteristics in the so-called "double bond" region should be discussed, especially because of the recent observations made by Chakravarti *et al.*[4] in case of arborine. It should, however, be borne in mind that the interpretation of the spectra of amides in the region 1500–1700 cm^{-1} is not simple.[4,6,7]

Chakravarti *et al.*[4] ascribed the band in the vicinity of 1531 cm^{-1} (6·52 μ) to $\rangle C{=}N$-linkage primarily because such a peak is invariably present in the 1,2-substituted-4-quinazolones and absent in the corresponding 2,3-dihydro compounds. Further, they conclude that the same band might as well arise from the system,



(Ar = aromatic ring).

The latter is more likely since if it were due to $\rangle C{=}N-$, the bond around 1531 cm^{-1} should also be exhibited by 2- and 4-quinazolones, 2-methyl-4-quinazolone and glycosminine (XIII; 2-benzyl-4-quinazolone). On the other hand, complications arise when the possible tautomeric forms of the compounds are considered instead of the preferred structures alone and, therefore, the explanation put forward is not satisfactory.

Inspection of Table 1 reveals that a strong band occurs between 1527–66 cm^{-1} (6·55—6·39 μ) in the N-substituted 4-quinazolones in which hydrogen bonding is not possible and is conspicuously absent in this region (most probably due to the expected frequency shift) in the compounds which are hydrogen bonded in their predominant forms, such as 2,3-dihydro-1,2-alkylated-4-quinazolones, glycosmicine (II; 1-methyl-2-keto-1:2-dihydro-4-quinazolone) and the compounds already mentioned. Culbertson *et al.*[7] earlier assigned the band in the region, 1593–1625 cm^{-1} to $\rangle C{=}N-$, but in the case of 2- and 4-quinazolones they considered the respective

bands at 1645 cm^{-1} (6·08 μ) and 1664 cm^{-1} (6·01 μ) instead of that at 1608 cm^{-1} common to both for the same function to explain the greater conjugation effect in the former. Similar lowering of frequency observed in glycorine (V; 1-methyl-4-quinazolone) in relation to the latter would tend to support this view. Except for the three compounds, no others show a third band in the region 1593–1704 cm^{-1} (6·28–5·87 μ) despite the fact that all contain the >C=N-grouping. On the other hand, the band between 1593 cm^{-1} and 1625 cm^{-1} is common to all so far studied (Table 1). Therefore, it seems reasonable to assign the two strong bands, one at 1626–1676 cm^{-1} (6·15 and 5·97 μ) and the other at 1593–1625 cm^{-1} (6·28 and 6·15 μ) to characteristics of the quinazolones. While the former is definitely due to N-acyl carbonyl, assignment of the latter to the entire conjugative system rather than any particular function (e.g. >C=N—) in the molecule would be more appropriate since the effects of the groups, individually or collectively, are not easily ascertainable. But such assignment also suffers from the defect that even 2,3-dihydro-1,2-alkylated-4-quinazolones in which the >C=N-group is reduced also absorb in this region though with less intensity. The possible explanation may be that (i) the C—N bond still retains enough double bond character or (ii) the >C=N-group of the tautomeric enolic form may come into play.[6a]

EXPERIMENTAL*

Synthesis of 1-*methyl-4-quinazolone* (*glycorine* V)

Anthranilamide (1·5 g) was prepared[15] from isatoic anhydride and ammonia and was N-methylated[16] with methyl iodide (1·5 cc) in a sealed tube for 6 hr on a steam bath. N-methyl anthranilamide (1 g), m.p. 160–161°, was refluxed with ethyl orthoformate (10 cc) and acetic anhydride (10 cc) for 2 hr under anhydrous conditions. After distillation of the excess reagents, ice was added, the pH adjusted (Na_2CO_3) to 10–11, and the mixture thoroughly extracted with chloroform, washed with the minimum amount of water, dried and evaporated. The crude product was converted into a *picrate* (0·6 g) in methanolic solution and after two recrystallizations from the same solvent, the yellow needles, m.p. 249° (dec) were obtained. (Found: C, 46·77; H, 3·16; N, 17·39. $C_{15}H_{11}N_5O_8$ requires: C, 46·27; H, 2·85; N, 17·99%). It was decomposed through a column of Amberlite IRA 400 ion-exchange resin and the free base transformed into its *hydrochloride* (0·2 g). The latter was crystallized from absolute alcohol and finally from alcohol–acetone in white needles, m.p. 242° (dec). (Found: C, 51·61; H, 5·48; N, 13·02. $C_9H_9N_2OCl\ 2/3H_2O$ requires: C, 51·80; H, 5·03; N, 13·43%). The hydrochloride showed an IR spectrum in KBr indistinguishable from that of glycorine hydrochloride (IX). The regenerated base on crystallizations from benzene (dried *in vacuo* at 80° immediately after filtration) showed no depression in mixture m.p. with an authentic sample of 1-methyl-4-quinazolone which in turn proved (mixed m.p. and N.M.R comparison) to be identical with glycorine (V).

Preparation of N^4-*phenylacetylanthranilamide*

Freshly prepared phenylacetylchloride (2 g) was gradually added under anhydrous condition to a constantly stirred solution of anthranilamide (1 g) in dry pyridine (8 cc) at 0° and the mixture left overnight at room temp. The product was then poured onto crushed ice and left 1 hr and the pH adjusted to 3 with conc HCl. The separated gummy substance was extracted with chloroform (200 cc), washed successively with 2 N HCl, saturated $NaHCO_3$ and water, dried (Na_2SO_4) and the solvent evaporated. The residue on masceration with benzene with occasional ice-cooling afforded an amorphous solid. The crude product on recrystallization from the same solvent yielded colourless rhombohedral crystals (1 g) m.p. 127°. (Found: C, 70·52; H, 5·53; N, 11·31. $C_{15}H_{14}N_2O_2$ requires: C, 70·86; H, 5·55, N, 11·02%).

* All m.p.'s are uncorrected.

Synthesis of 2-benzyl-4-quinazolone (glycosminine XIII)

N^4-phenylacetylanthranilamide (0·4 g) was heated for 2 hr in an oil-bath at 170–190°. The cooled product on crystallization from absolute alcohol afforded 2-benzyl-4-quinazolone (0·15 g) in fine white needles, m.p. 249°. (Found: C, 75·99; H, 5·22; N, 11·61. $C_{15}H_{12}N_2O$ requires: C, 76·24; H, 5·12; N, 11·85%). The yield was dependent on the time and temp of the reaction. The synthetic base showed no depression in m.p. when admixed with a sample of glycosminine (XIII) and gave an IR spectrum identical with the latter.

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