2.5 g of 1,6-dinitrophenazine which was recrystallized from glacial acetic acid, mp 348–349 °C (lit.[7] 343 °C). The third yellow band contained a mixture of 1,6- and 1,9-dinitrophenazine. It was rechromatographed yielding 0.5 g of 1,6-dinitrophenazine and 1.5 g of 1,9-dinitrophenazine which was recrystallized from 50% aqueous acetic acid, mp 267–270 °C (lit.[7] 273 °C). 1,6-Dinitrophenazine, λ_{max} (EtOH) 246, 365 nm.

1,6-Diaminophenazine. 1,6-Dinitrophenazine (816 mg) was suspended in 230 ml of 90% aqueous acetic acid, according to the literature.[7] At the boiling temperature 1.8 g of zinc powder was added with stirring in small portions over a period of 1.5 h. At the end of this period the dark red solution turned brown. Another 300 mg of Zn powder was added over 5 min. The solution was filtered and diluted with 230 ml of water. Concentrated ammonium hydroxide was added to pH 8 and the red precipitate was allowed to form during 24 h at 0 °C. It was taken up in 100 ml of 2% hydrochloric acid, boiled for 2 h, treated with a little Norit, and filtered. Neutralization with concentrated ammonium hydroxide gave 632 mg of a red precipitate which was recrystallized twice from ethanol: yield 473 mg (75%) of 1,6-diaminophenazine; mp 250 °C (lit.[7] 245 °C), TLC (silica gel), chloroform/methanol (9:1), R_f 0.55; λ_{max} (EtOH) 242, 290, 357, 377, 512 nm. The electronic spectrum did not change upon addition of sodium sulfite or sodium borohydride. Also in warm Me_2SO the spectrum remained the same.

Registry No.—2-Nitrodiphenylamine-6,2′-dicarboxylic acid, 58718-49-3; iodinin, 68-81-5; 2-chloro-3-nitrobenzoic acid, 3970-35-2; anthranilic acid, 118-92-3.

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Studies on 4-Quinazolinones. 8.[1] Mechanism of Chromic Acid Oxidation of Arborine[2]

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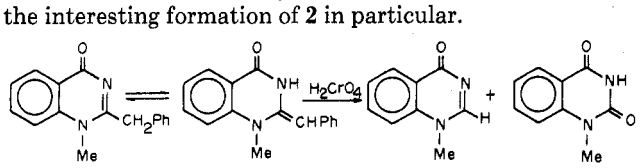
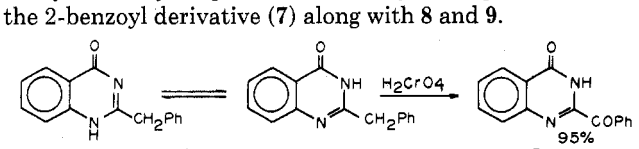
Plausible mechanisms of formation of **2** and **3** from **1** by chromic acid oxidation have been advanced. A novel hydride shift from the side chain to the nucleus, or protonation across C=C in the alkene form, has been envisaged in the conversion of **1** to **2**. Oxidation of a number of 1,2- and 2,3-disubstituted and 2-monosubstituted alkyl/aryl derivatives of 4-quinazolinone has also been studied and the formation of various products explained.

It was earlier reported[4] that arborine (**1**),[5] the major 4-quinazolinone alkaloid of *G. arborea* (Roxb.) DC. (Rutaceae), underwent facile oxidation on brief heating with chromic acid in glacial acetic acid to glycorine (**2**) and glycosmicine (**3**), the co-occurring[6] minor bases in 78 and 14% yields, respectively. In view of the biogenetic implications,[7] we have studied this reaction in more detail to gain insight into the mechanism of the interesting formation of **2** in particular.

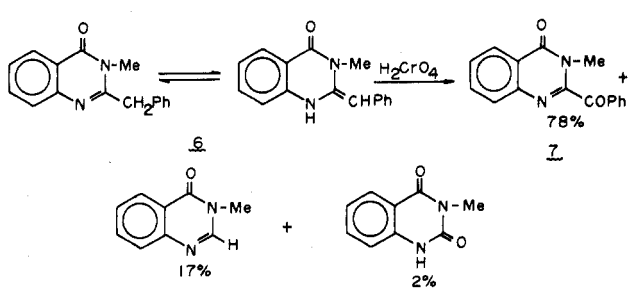


1a **1b** **2** **3**

The same reaction could also be brought about to the extent of 50% by heating with aqueous chromic acid, while chromic oxide in pyridine at room temperature afforded **3** and benzaldehyde. On the other hand, glycosminine (**4**) upon heating with chromic acid in glacial acetic acid furnished the expected 2-benzoyl-4-quinazolinone (**5**) as the sole product while 2-benzyl-3-methyl-4-quinazolinone (**6**) yielded predominantly the 2-benzoyl derivative (**7**) along with **8** and **9**.



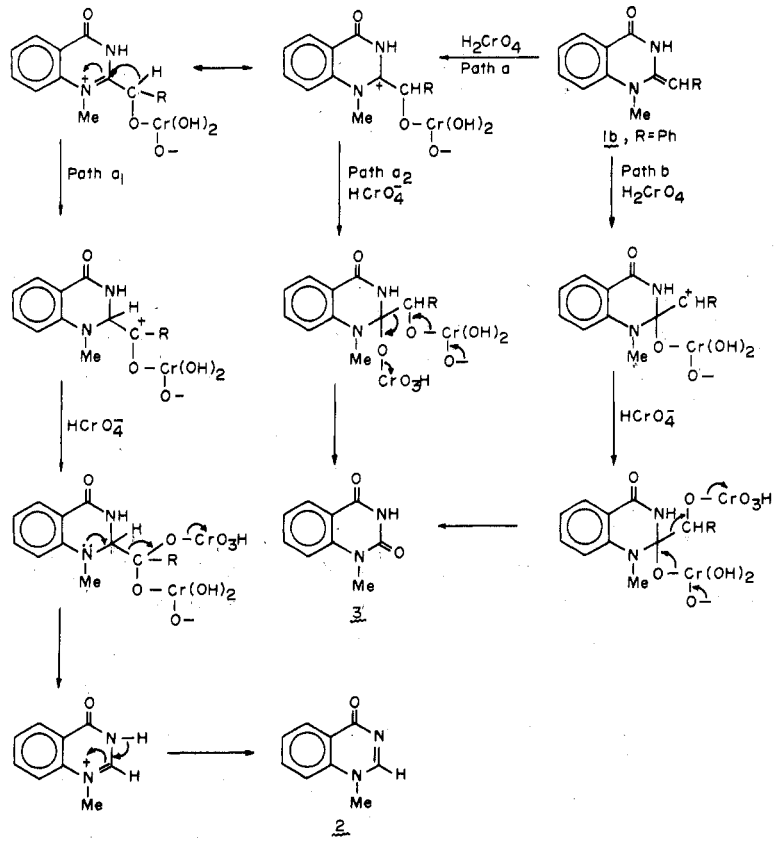
4 **5**



6 **7** **8** **9**

Conceivably, the oxidation of **1** to **2** with chromic acid involves the benzylidene form of arborine (**1b**), which almost certainly[5,8] takes part in all the oxidative processes studied so far,[4,5,9,10] and the inductive effect of the N-1 alkyl group. Should the benzylic form **1a** be involved, glycosminine, definitely shown[8] to exist in this form (**4**) only, would have furnished benzoyleneurea (**13**) as one of the products, contrary to the observation. Furthermore, oxidative debenzylation of **6**, though less favored, also indicated the participation of the lone pair of electrons on nitrogen. A plausible mechanism put forward in Scheme I involves an initial electrophilic addition of H_2CrO_4 to the benzylidene double bond of **1b**, analogous to that suggested[11,12] for the oxidation of alkenes. Attachment of the reagent at the benzylic carbon (path a) followed successively by a hydride shift[13] (path a_1), further attack by the oxidant, and cleavage of C–C bond could then form **2**. On the

Scheme I



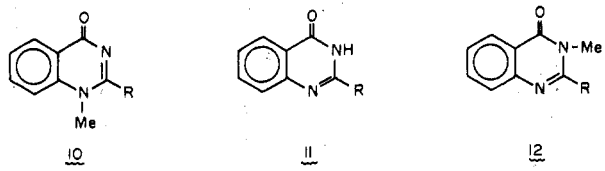
other hand, attachment of the second chromate ion at C-2 without prior hydrogen transfer (path a_2) or initial addition of the reagent at the same position (path b) followed by another chromate ion attack would lead to **3**. In any case, the reduction of chromium valency provides the driving force for the bond rupture.

In order to substantiate the proposed mechanism, we extended the original reaction to various other alkyl/aryl substituted 4-quinazolinones. The results summarized in Table I show that while 1,2-dialkyl derivatives (**10**) furnished **2** and **3** in varying amounts, the 2-alkyl derivatives (**11**) afforded products depending on the nature of the substituents. On the other hand, the 2,3-dialkyl derivatives (**12**) showed properties of both 1,2-disubstituted (**10**) and 2-monosubstituted (**11**) derivatives, the products and their yields being dependent on the substituent at position 2.

It can be seen from Table I that **2** is the major product from **10a** and **10b** wherein the hydride shift is possible (path a_1), with its maximum yield from **10b** due to better stability of its alkene form. The principal product **3** from **10c** and **10f** with no available hydrogen for transfer could easily be explained through path a_2 or b (Scheme I). On the other hand, the forced oxidative decarboxylation of the N-1 methyl group in **10d** in ca. 60% yield provided additional support to the participation of the alkene form in the reaction. Again, while the formation of **2** from **10c** and **10d** in small amounts could plausibly involve methyl migration (with concomitant attack by chromate ion in case of **10d**)[15] followed by oxidation of the resulting **10a**, it would be difficult to rationalize its formation from **10f** assuming phenyl migration since the 1-methyl-2-phenyl derivative (**10g**) did not provide **2** even under more drastic conditions. Besides, hydride shift in complete exclusion of methyl or phenyl transfer has been shown[14] in simpler systems like 2-phenylpropene and 2,2-diphenylethylene. The migration of methyl/phenyl in our system was also believed to be very unfavorable, if not altogether impossible. Furthermore, none of the reaction paths discussed above could satisfactorily explain the 18% yield of **3** from **10d**.

We, therefore, considered protonation prior to chromate

Table I. Chromic Acid Oxidation Products of Substituted 4-Quinazolinones



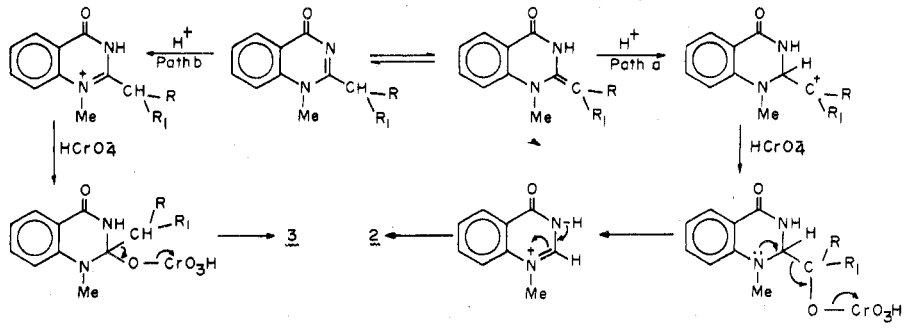
10 11 12

a, R = Me; b, R = Et; c, R = $CHMe_2$; d, R = CMe_3; e, R = H; f, R = $CHPh_2$; g, R = Ph; h, R = COMe; i, R = $C(OH)Me_2$; j, R = $C(OH)Ph_2$.

Compd	Products (%)		
10a	**2** (29)	**3** (11)	
10b	**2** (65)	**3** (7)	
10c[a]	**2** (1)	**3** (71)	
10d[a]	**2** (5)	**3** (18)	**11d** (60)
10f[a]	**2** (5)	**3** (82)	
2		**3** (9)	
11a	**11e** (29)		
11b	**11e** (8)		**11h** (27)
11c		**13** (36)	**11i** (46)
11d	No reaction		
11e[b]		**13** (5)	
11f		**13** (9)	**11j** (42), **5** (10), benzophenone (25)
11i		**13** (25)	
11j		**13** (6)	**5** (12), benzophenone (13)
12a	8 (20)	**9** (28)	
12b	8 (45)	**9** (4)	**12h** (31)

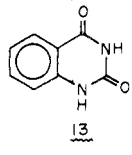
[a] Reaction time 0.5 h against 3 h for the rest. [b] Reaction time 48 h.

Scheme II



ion attack also as a distinct possibility. Thus, protonation across the alkene double bond in **10c** and **10f** would lead to **2** while protonation at N-3 would eventually yield **3** from all the compounds discussed above (Scheme II).

We also took into account the possibility of even partial conversion of **2** to **3**, in view of the reported[17,18] oxidation of **11e** to **13** in 5% yield on prolonged (7 days) reflux. This,



however, appeared unlikely because no such conversion could be detected after 0.5 h of reaction required for the complete transformation of **1** with ca. 14% yield of **3**. Nevertheless, the latter could be obtained from **2** in ca. 9% yield in 3 h. In any case, the more facile oxidation of **2** compared to **11e** further supported the postulated inductive effect of the N-1 methyl group and the mechanism could be explained through initial protonation at N-3 (path b, Scheme II).

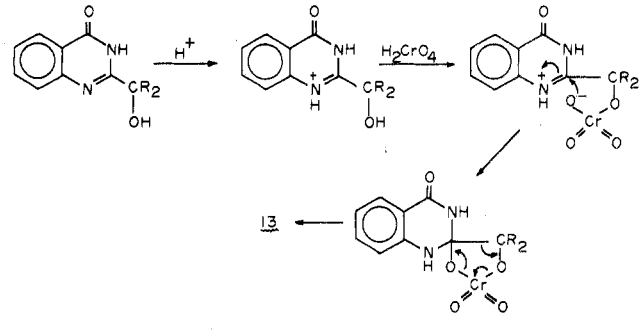
Now, in order to distinguish between the alternative postulates, viz. hydride transfer (Scheme I) or protonation (Scheme II), we performed the following experiments. Arborine (**1**), both unlabeled and deuterated (with MeOD in the presence of sodium) at the benzylic methylene (d_0, d_1, d_2; *m/e* 250, 251, 252), on being treated separately with chromic acid in DOAc (using D_2O for working up), afforded **2** and its deuterated product (glycorine-d_0, -d_1; *m/e* 160, 161). On the other hand, replacement of DOAc with HOAc yielded unlabeled **2**. The results would apparently support the protonation postulate. However, labeled **1** itself when heated on a steam bath with HOAc alone for 0.5 h or **2** on treatment with DOAc under the same condition exchanged[19] deuterium. These results did not allow us to arrive at a definite conclusion.

Nevertheless, as has already been discussed, none of the postulates alone could explain the formation of the products of all the 4-quinazolinone derivatives studied. We, therefore, believe that both the reaction pathways compete with each other. The relative contribution of each would conceivably depend on the stability of the intermediate carbonium ion and as such on the structure of the individual compounds used.

It now remains to explain the oxidation products of N-unsubstituted 2-alkyl-4-quinazolinones (Table I). Formation of **11e** from **11a** in reasonable yield apparently proceeds through oxidative decarboxylation (cf. quinaldic acid[16]) of the C-2 methyl group. 2-Ethyl-4-quinazolinone (**11b**), like its benzyl analogue (**4**), underwent expected oxidation to the 2-acetyl derivative (**11h**) as the major product which by further oxidative decarboxylation could lead to **11e**.

On the other hand, 2-isopropyl- (**11c**) and 2-diphenylmethyl- (**11f**) 4-quinazolinones afforded benzoyleneurea (**13**) and the corresponding 2-(1′-hydroxy) derivatives (**11i** and **11j**)[20] in fairly good yields. The intermediacy of the latter envisaged (Scheme III) in the formation of **13** could be confirmed by bringing about the same transformation directly

Scheme III



from **11i** and **11j** under identical condition. The additional product, viz. 2-benzoyl-4-quinazolinone (**5**),[21] obtained in ca. 10% yield from **11f** could presumably be derived also from the intermediate **11j** by further oxidation, analogous to the conversion of triphenylcarbinol to benzophenone.[22] As expected, 2-*tert*-butyl-4-quinazolinone (**11d**) did not undergo oxidation at all.

In conclusion, chromic acid oxidation, like metal hydride reduction,[21,23-25] once again demonstrates the unpredictable and yet most fascinating course of reactions of the 4-quinazolinone system.

Experimental Section[26]

General Procedure for Oxidation with Chromium Trioxide in Acetic Acid. The 4-quinazolinone derivatives were prepared by known methods. Each compound to be oxidized was dissolved in a minimum volume of glacial acetic acid and heated with 2 molar equiv of CrO_3 over a steam bath for the period specified in Table I. The reaction mixture was then cooled, diluted with water, basified with ammonia, and extracted with chloroform.

Glycorine (**2**) could be quantitatively isolated from the aqueous part by evaporating it to dryness and extraction of the residue with hot chloroform. It was characterized as picrate,[8] mp 249 °C dec.

Benzoyleneurea (**13**), mp 342–343 °C, was isolated as a crystalline solid in most cases on dilution of the reaction mixture with water and cooling. In the cases of **11f** and **11j**, however, it was isolated from the aqueous part on cooling after solvent extraction.

All other crude products from the chloroform extract were separated and purified through chromatography over silica gel or alumina (neutral) followed by crystallization. The yields are given in Table I and the physical data of the products other than those reported earlier are mentioned below.

2-Benzoyl-4-quinazolinone (**5**): mp 179–181 °C; ir 3130 sh, 3030, 1706, 1680, 1600 sh, 1597 cm^{-1}.

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.88; H, 3.98; N, 11.05.

2-Benzoyl-3-methyl-4-quinazolinone (**7**): mp 137 °C; ir 1700 sh, 1675, 1663, 1582 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.47; N, 10.67. Found: C, 72.55; H, 4.56; N, 10.44.

2-Acetyl-3-methyl-4-quinazolinone (**12h**): mp 78–79 °C; ir 1712, 1665, 1605, 1583 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.54; H, 5.08; N, 13.59.

2-(1′-Hydroxyisopropyl)-4-quinazolinone (**11i**): mp 148 °C; ir 3350, 3230, 3100, 1660, 1606 cm^{-1}; NMR δ 1.73 s (6 H, Me_2), 4.9 br (OH), 7.25–7.85 m (3 H, ArH), 8.28 d (1 H, J = 7 Hz, C_5H).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.72; H, 5.93; N, 13.72. Found: C, 64.94; H, 6.06; N, 13.58.

Synthesis of 2-(1′-Hydroxyisopropyl)-4-quinazolinone (11). A solution of anthranilamide (0.92 g) in dry pyridine (2 ml) was treated with 2-bromoisobutyryl bromide (1.2 ml) at 0 °C and the reaction mixture was kept at room temperature for 12 h. Crushed ice was added to it and the separated solid (1.34 g) was filtered, washed, and dried. On repeated crystallizations from benzene–alcohol it afforded N-(α-bromoisobutyryl)anthranilamide, mp 191–192 °C.

Anal. Calcd for $C_{11}H_{13}N_2O_2Br$: C 46.35; H, 4.60; N, 9.83; Br, 28.04. Found: C, 46.45; H, 4.57; N, 9.65; Br, 28.00.

N-(α-Bromoisobutyryl)anthranilamide (0.1 g) was dissolved in 50% aqueous methanol (5 ml) and heated over a steam bath with ammonia solution (5 ml) until all the solvent was evaporated. The residue on purification through chromatography and crystallization from benzene–petroleum ether afforded **11i** as colorless needles, mp 147–148 °C, identical (melting point, mixture melting point, ir, TLC) with the oxidation product of **11c**.

Acknowledgment. We are grateful to the Council of Scientific and Industrial Research, New Delhi, for a senior fellowship to one of us (S.C.) and to Dr. Nitya Nand, CDRI, Lucknow, for the NMR spectrum.

Registry No.—**1,** 6873-15-0; **2,** 3476-68-4; **2** picrate, 58718-50-6; **3,** 604-50-2; **5,** 13182-47-3; **7,** 13182-48-4; **10a,** 7471-65-0; **10b,** 10553-04-5; **10c,** 58718-51-7; **10d,** 58718-52-8; **10f,** 59123-36-3; **11a,** 1769-24-0; **11b,** 3137-64-2; **11c,** 13182-64-4; **11e,** 491-36-1; **11f,** 18963-84-3; **11i,** 52827-42-6; **11j,** 18963-82-1; **12a,** 1769-25-1; **12b,** 58718-53-9; **12h,** 58735-56-1; **13,** 86-96-4; chromium trioxide, 1333-82-0; anthranilamide, 88-68-6; 2-bromoisobutyryl bromide, 563-76-8; N-(α-bromoisobutyryl)anthranilamide, 58718-54-0.

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(26) All melting points were determined in open capillaries and are uncorrected. The ir spectra were taken in Nujol mull in a Perkin-Elmer Infracord spectrophotometer (Model 137). The NMR spectrum of **11i** was recorded in a 60-MHz Varian instrument in $CDCl_3$ with Me_4Si as internal standard. Silica gel or alumina (neutral) was used for column chromatography. Thin layer chromatography was done on 0.3 mm silica gel plates using ethyl acetate–formic acid–chloroform (4:1:5) as the solvent system and the spots were developed by iodine vapor. Microanalyses were done by Dr. R. D. Macdonald, Micro-Analytical Laboratory, University of Melbourne, Australia. Identity of the oxidation products were established by comparison (melting point, mixture melting point, ir, TLC) with the authentic specimens or with those prepared according to procedures reported in the literature.