Heterocyclic Compounds with a Bridgehead Nitrogen Atom. Synthesis in the Imidazo[1,2-*c*]quinazoline Series

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The structures of imidazo[1,2-*c*]quinazolines were reexaminated and established by spectroscopic studies with the aid of high-field ^1H and ^{13}C nmr and mass spectra. In acidic media, **3** reacts to give the products of electrophilic substitution reaction and ring opening compound **5**, leading to the imidazo[1,2-*c*]benzo[*e*]-[1,2,3]triazine ring.

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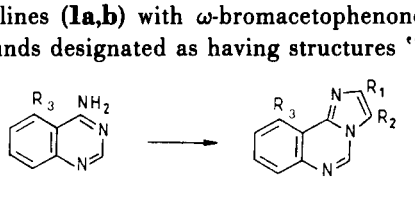
Introduction.

Different derivatives involving the [1,2-*a*]imidazole moiety: dipyrido[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-1, Glu-P-2) [1], their benzo derivatives pyrido[1′,2′:1,2]imidazo[5,4-*c*]-isoquinoline [2] and imidazo[4,5-*f*]quinoline [3] have been investigated as mutagenic compounds. The nature of different substituent groups in the basic ring influenced markedly the mutagenicity which is increased when the amino derivatives were further substituted by methyl groups [1]. In continuation of our studies on the nitrogen bridgehead azaindolizines, we have now investigated the imidazo[1,2-*c*]quinazoline series which have been briefly explored [4]. In this midst of this activity, these appeared two reports describing the condensation of 4-aminoquinazolines (**1a,b**) with ω-bromacetophenones to give compounds designated as having structures "**2a**" [5].



1a-b 2a-d

2a R_1 = H, R_2 = *p*$OCH_3C_6H_4$, R_3 = 9-CH_3
2b R_1 = *p*$OCH_3C_6H_4$, R_2 = R_3 = H
2c R_1 = CO_2Et, R_2 = R_3 = H
2d R_1 = R_3 = H, R_2 = CO_2Et

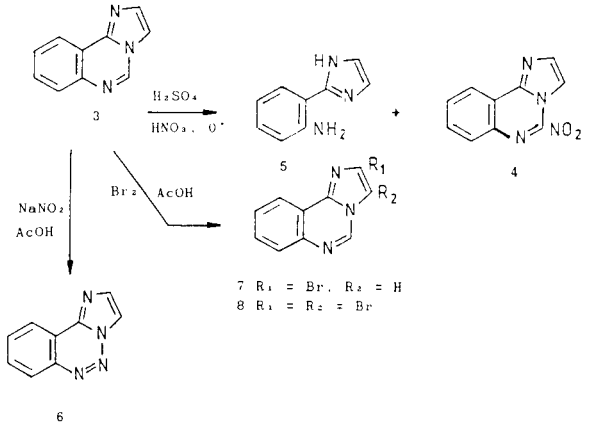
However, our attempts to nitrosate or brominate **2b** disagreed with the expected 2-position with a deshielding of the singlet H3 (or H5) suggesting a peri effect. On the other hand, two isomeric esters **2c** and **2d** were isolated from the reaction of **1a** with ethyl bromopyruvate. In view of the fact that in contrast, 2-aminopyridine gives the 2-functionalized imidazo[1,2-*a*]pyridine system [6], with electrophilic substitution reaction at the C3 position in accord with a quantum approach [7], we decided to investigate the results of the condensation reactions in an one step from 4-aminoquinazoline (**1a**). In this paper we describe the structural determination on the basis of the reactivity of this heterocyclic system.

4-Aminoquinazoline (**1a**) was prepared by condensation of anthranilonitrile with formamidine acetate in refluxing dry ethoxyethanol for one hour, in a 97% yield. The reaction of **1a** with bromacetaldehyde gave **3** in 64% yield.

Assignment of the proton signals of **3** offers more difficulty because the overlaps of the imidazole and benzene signals. From the high resolution COSY-45 [9] spectrum it appears that the proton absorbing at δ 7.54 shows a weak coupling (1.5 Hz) with the proton at δ 7.56 are due to H2 and/or H3. Protons absorbing at δ 7.61 and 7.57 are due to H8 and/or H9 and the chemical shifts of the adjacent protons at δ 7.84 and/or 8.44 can be assigned to H7 and/or H10. The singlet signal which resonates at 8.79 ppm is easily assigned to H5. This assignment is completed by performing the long-range shift correlation experiment (LR-HETCOR) [10]. From the normal HETCOR ^{13}C-^1H correlation experiment, the carbon signal which resonates at the highest field δ 113.4 is easily assigned to C3 by camparison with assignments for imidazopyridine [11], and also differentiates H2 and H3 (δ 7.54 and 7.56 respectively). In addition, the C10a signal can be located at δ 119.5, consistent with the β effect of N1, N4 and N6 atoms. The observation of long-range $^3J_{CH}$ couplings in the LR-HETCOR was optimized as 8 Hz and allows us to clarify the ambiguity of the benzene system. The carbon signals which reasonate at δ 128.62 and 128.25 are assigned to C9 and C7, respectively, because the C10a peak shows the expected three-bond C-H coupling with H9 and H7. Consistent with these assignments H8 and H10 also show $^3J_{CH}$ coupling with C6a and differentiate the two quaternary carbons at C6a and C10b at δ 140.71 and

141.42, respectively. The complete proton and carbon chemical shifts of **3** are reported in the experimental.

Nitration confirms the structural assignments of **3**. The peri effect in the chemical shift of H3 due to the nitro group of **4** indicated C5 as the site of electrophilic reaction. The poor yield (16%) of **4** resulted in the use of acid media as described by Cardellini [4c] and gave the ring opening compound **5**. We anticipated the formation of a triazine ring system in the nitrosation reaction of **3**. As expected, **3** undergoes ring-opening, ring-closure reaction with sodium nitrite and acetic acid at room temperature



over 2 hours to give the imidazo[1,2-*c*]benzo[*e*][1,2,3]-triazine (**6**) (40%) as a yellow crystalline solid; ms: m/z 170 (M^+, 15.6) and 142 ($M-N_2$, 100). The "COSY" spectrum gives H2 (7.66), H3 (8.25), H7 (8.33), H8 (7.78), H9 (7.87), H10 (8.46) connectivities, consistent with results obtained in correlation experiments (^{13}C-^1H and LR-HETCOR).

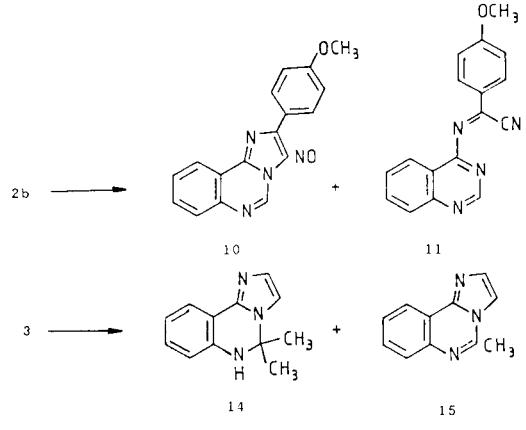
In contrast to the reactivity of the imidazo[1,2-*a*]pyridine structure, treatment of **3** with 1 mole of bromine in acetic acid or with *N*-bromosuccinimide (NBS) in carbon tetrachloride yield a mixture of materials which was shown to consist of two basic products as mono and dibromide **7** and **8** identified by the mass spectra with m/z 247-249 and 325, 327 and 329 respectively. Comparison of the spectral data of **3** with those of **7** and **8** leads to the unequivocal assignments of the resonances of the substituted positions C2 and C2-C3: both resonances are shifted upfield by 6/9 ppm, with a δ CH 111.27 for C3 and a quaternary signal at δ 122.14 for C2 in **7** and two quarternary signals for **8** at δ 96.04 and 123.72 characteristic of C2-C3.

The reaction of 4-aminoquinazoline (**1a**) under strictly anhydrous conditions in ethanol with an excess of 4'-methoxyphenacyl bromide provided 4-(4'-methoxyphenacylamino)quinazoline (**9**) and the tricyclic structure **2b** in 54 and 19% yield, respectively. As expected, the ^1H nmr signal of **10** resulting of the nitrosation of **2b** showed a marked downfield shift of the signal of H5, consistent with the electrophilic site at the 3-position, and demonstrated the 2-position of the phenyl ring moiety. Interestingly, when **10** was subjected to chromatography on a neutral alumina column with elution with dichloromethane, the ring-opening quinazolylbenzimidoyl cyanide **11**, m/z 288 was found, in accord with the ring opening reaction of nitrogen bridgehead compound [12]. The nitration of **2b** at 0° yielded (66%) exclusively the 3',5'-dinitro compound **12**, m/z 365 (M^+, 100) (see Experimental). No opening-ring compound was isolated in contrast with the nitration of **3**. When **2b** was brominated and the initial salt treated with sodium carbonate, the 3-Br derivative **13** was isolated in 72% yield.

The reaction of equimolar quantities of **1a** and ethyl bromopyruvate in ethanol gave a moderate yield of the ester derivative and a by-product separable by chromatography. The minor product (14%) was recognised as the 2-ethyl carboxylate derivative **2c** by the presence, in its ^1H nmr spectrum of a high frequency singlet (δ 9.85) due to H5 which is deshielded by the adjacent carbonyl group. The major product (74%) was then clearly the ethyl 3-carboxylate **2d**. Azaindolizines were found to undergo ring-opening, ring-closure reactions [8]. In order to be sure that no Dimroth rearrangement had occured during the cyclisation treatment at 80° in ethanol, the condensation reaction was carried out at intervals of 1 hour, 3 hours and 10 hours to give **2c** and **2d**. The ^{13}C data of **2c** and **2d** were also in agreement with the data of the imidazo[1,2-*a*]pyridine and pyrimidine ring systems [11,13].

The mutagenicity of the imidazo[1,2-*a*]pyridine moiety is increased when these structures were further substituted by methyl groups. The *C*-methylation [15] by a homolytic process generated from *t*-butyl hydroperoxide and catalysed by ferrous ion in sulfuric acid media with **3** was studied.

Two compounds in addition to the starting material were obtained. One of the products was identified as the 5,6-dihydro-5,5-dimethylimidazo[1,2-*c*]quinazoline (**14**) in 5% yield. The second product was recognised as the 5-methylimidazo[1,2-*c*]quinazoline (**15**) in 27% yield by the presence, in its ^1H nmr spectrum of a singlet (δ 2.87, 3H), identified by comparison with an authentic sample.



EXPERIMENTAL

General Details.

Melting points were taken on a Büchi capillary apparatus and are not corrected. Infrared spectra were recorded on a Beckman AccuLab 2. Proton nmr spectra were recorded with a Bruker WM 300 (300 MHz FT), MSL 300 (300 MHz FT) or Varian 360 (60 MHz) spectrometers. Carbon nmr spectra were performed on a Bruker MSL 300 instrument operating at 75 MHz. The ^{13}C chemical shifts are reported in ppm from TMS with the center ^{13}C resonance of deuteriochloroform as an internal reference for ^{13}C (77.0 ppm) and with the small amount of residual chloroform as an internal reference from the proton spectrum (7.24 ppm). COSY spectra were obtained by using Jeener's two-pulse sequence 90°t_1-Pw-acquire. The mass spectra were recorded with a Jeol JMS DX 300 instrument or a LKB 2091 spectrometer. Compounds were purified by high-performance liquid chromatography (hplc), Jobin-Yvon, on a preparative alumina column using Merck alumina (70-230 Mesh). Reaction was monitored with a hplc Waters M-6000A, uv detector model 340 working at 254 nm with a RP18 Lichrosorb^R 50334 (Hibar) analytical column, 25 cm, 10 μ, eluting with methanol or methanol-water: 80-20. Time retention was expressed in minutes. Compounds were purified on a neutral alumina column using Merck alumina (70-230 Mesh).

4-Aminoquinazoline (**1a**).

Forty g (0.339 mole) of anthranilonitrile was dissolved in 400 ml of ethoxyethanol, then 73 g of formamidine acetate (0.673 mole) was added. The mixture was refluxed for 1 hour. After cooling, the precipitate was filtered, washed with ethoxyethanol and dried at 50°, to give 28 g of **1a**. The filtrate was evaporated *in vacuo*, and the crude material was suspended in ether and filtered. The precipitate was washed with ether and dried to give 19.4 g of (**1a**) identical to the first sample, total yield 47.4 g (97%), mp 267-269°, (Lit [16] 268-269°).

2-(4'-Methoxyphenyl)imidazo[1,2-*c*]quinazoline (**2b**).

To 12 g of **1a** (82.7 mmoles) dissolved in dry ethanol (1.51) was added 30 g of 4'-methoxyphenacylbromide (131 mmoles) in 100 ml of anhydrous ethanol. The mixture was refluxed for 4 hours. After cooling the solution was filtered off to give 13 g (54%) of 4-(4'-methoxyphenacylamino)quinazoline, mp 259-261°; ms: 293 ($M^{+\cdot}$, 17%), 275 (12), 260 (7), 232 (2), 135 (100), 77 (21); ir (potassium bromide): cm^{-1}, NH (3250), C-H_{arom} (3050), C=O (1660), C-O-C (1240). The filtrate was evaporated, diluted with water, and made alkaline with sodium carbonate. The solid which separated, was filtered to give 2 g of the starting amine **1a**. The aqueous layer was extracted with methylene chloride, dried, and evaporated *in vacuo*. The residual oil was submitted to chromatography on neutral alumina. Elution with methylene chloride gave 4.4 g of **2b** as a white powder who became green on light (19%), mp 185-187°; ^1H nmr (deuteriochloroform): 60 MHz, δ 3.83 (s, OCH_3), 6.95 (d, H3', 5', J = 9 Hz), 7.67 (m, H2, 7, 8, 9), 7.93 (d, H2', 6', J = 9Hz), 8.57 (m, H10), 8.78 (s, H5); R_f (methanol, 0.5 ml/min) = 9 mn 06 s.

Anal. Calcd. for $C_{17}H_{11}H_3O$: C, 74.18; H, 4.00; N, 15.27. Found: C, 73.96; H, 4.17; N, 15.32.

Ethyl Imidazo[1,2-*c*]quinazoline-2-carboxylate (**2c**) and Ethyl Imidazo[1,2-*c*]quinazoline-3-carboxylate (**2d**).

Fifty g of ethyl bromopyruvate (0.256 mmole) in 400 ml of dry ethanol were added to 17 g (0.117 mole) of **1a**. The mixture was refluxed for 4 hours until no evolution was found by hplc. After cooling the solution was filtered to give 15 g of **1a**. The solution was evaporated, poured into water and basified with concentrated sodium carbonate solution. The solid which separated was filtered and identified as the starting amine **3g**. The aqueous layer was extracted with dichloromethane and chromatographed on a neutral alumina column. Elution with methylene chloride gave 1.2 g of **2d** as a white powder (4.2%), mp 155-157°; ^1H nmr (deuteriochloroform): 300 MHz, δ 1.45 (t, CH_3), 4.46 (a, CH_2), 7.71 (td, H8), 7.79 (td, H9), 8.02 (dd, H7), 8.24 (s, H2), 8.57 (dd, H10), 9.85 (s, H5); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 14.46 (CH_3), 61.64 (CH_2), 117.66 (C3), 118.67 (C10a), 123.54 (C10), 128.63 (C7), 129.11 (C9), 131-60 (C8), 137.33 (C2), 140.15 (C5), 141.60 (C6a), 146.51 (C10b), 160.14 (C=O); ms: (EI), 241 ($M^{+\cdot}$, 95%), 213 ($M^{+\cdot}$ - OEt, 38), 196 (66), 169 (100), 149 (19), 141 (33), 135 (31) 129 (52), 121 (21), 114 (27), 107 (18), 102 (21), 77 (13), 76 (11); ir (potassium bromide): cm^{-1}, C=O (1700), C-N=C (1625), C-O-C (1225).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56; N, 17.43. Found: C, 64.52; H, 4.73; N, 17.30.

Further elution gave 400 mg of (**2c**) as pale yellow crystals (1.4%), mp 169-171°; ^1H nmr (deuteriochloroform): 300 MHz, δ 1.44 (t, CH_3), 4.48 (q, CH_2), 7.67 (td, H8), 7.76 (td, H9), 7.94 (dd, H7), 8.25 (s, H3), 8.63 (dd, H10), 8.90 (s, H5), ^{13}C nmr (deuteriochloroform): 75 MHz, δ 14.27 (CH_3), 61.49 (CH_3), 61.49 (CH_2), 116.60 (C3), 119.50 (C10a), 123.51 (C10), 128.65 (C7), 129.26 (C9), 130.96 (C8), 136.57 (C5), 136.90 (C2), 141.11 (C6a), 141.71 (C10b), 162.63 (C=O); ms: (EI) 241 ($M^{+\cdot}$, 37%), 213 (M^+ - OEt, 5), 196 (34), 169 (100), 141 (19), 129 (42), 114 (19), 102 (16), 76 (11), 75 (13); ir (potassium bromide): cm^{-1}, C=O (1700), C-N=C (1625), C-O-C (1225).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56; N, 17.43. Found: C, 64.58; H, 4.71; N, 17.36.

Imidazo[1,2-*c*]quinazoline (**3**).

Bromacetaldehyde diethylacetal (54.4 g, 0.276 mole) was refluxed for 30 minutes in 50 ml of aqueous hydrochloric acid (40:10 v/v). After cooling, bromacetaldehyde was extracted with ether and was added dropwise to a solution of 20 g (0.138 mole) of **1a** in 800 ml of dry ethanol, and the mixture was refluxed for 4 hours. After cooling the suspension was filtered. The filtrate was evaporated *in vacuo*, dissolved in water and made alkaline with sodium carbonate. The solid formed was filtered and found to be starting amine **5g**. Aqueous layers were extracted with methylene chloride, washed with calcium chloride and evaporated. The residue was chromatographed eluted with dichloromethane to give 15 g of **3** as white platelets (64%), mp 135-137° (Lit [1] 127-129°); ^1H nmr (deuteriochloroform): 300 MHz, δ 7.54 (d, J = 1.5 Hz, H2), 7.56 (d, H3), 7.57 (td, $J_{7,8}$ = 7 Hz, $J_{8,9}$ = 6 Hz, $J_{8,10}$ = 2 Hz, H8), 7.61 (td, $J_{7,9}$ = 2 Hz, $J_{9,10}$ = 6 Hz, H9), 7.84 (dd, H7), 8.44 (dd, H10), 8.79 (s, H5); ^{13}C nmr (deuteriochloroform): 75 MHz): δ 112.00 (C3, J = 194 Hz), 119.50 (C10a), 122.48 (C10, J = 163.5 Hz), 128.25 (C7, J = 163.5 Hz), 128.62 (C9, J = 163.5 Hz), 129.96 (C8, J = 163.5 Hz), 132.74 (C2, J = 192.0 Hz), 136.79 (C5, J = 209 Hz), 140.71 (C-6a), 141.42 (C-10b); ms: (EI) 169 ($M^{+\cdot}$, 100), 142 (M^+ - HCN, 17), 115 (M^+ - 2HCN, 8), R_f (methanol-water: 80/20, 0.5 ml/min) = 8 mn 12 s.

5-Nitroimidazo[1,2-*c*]quinazoline (**4**) and 2-(*o*-Amino-phenyl)-imidazole (**5**).

Five hundred mg of **2** (2.96 mmoles) was dissolved in 10 ml of concentrated sulfuric acid cooled to -10° without rising above 0°. When the solution was again at -10°, 1 ml of nitric acid (d = 1.38) was added until the temperature rose to -2°. The solution was stirred 1 hour at 0° and then allowed to stand 2 hours at 20°. After this time the solution was poured into 50 g of ice and then basified with sodium carbonate. The aqueous layer was extracted with methylene chloride and dried. After evaporation the residue was chromatographed on neutral alumina and eluted with dichloromethane.

The first product obtained was 5-nitroimidazo[1,2-*c*]quinazoline (**4**) as a yellow powder (100 mg, 16%), mp 109-111°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.76 (d, J 1.5 Hz, H2), 7.70 (td, H8), 7.99 (td, H9), 8.31 (d, H3), 8.44 (dd, H7), 8.65 (dd, H10); ms: (EI) 214 ($M^{+\cdot}$, 24%), 168 ($M-NO_2$, 9), 142 (100), 129 (28), 102 (54).

Anal. Calcd. for $C_{10}H_6N_4O_2$: C, 56.07; H, 2.80; N, 26.17. Found: C, 56.25; H, 2.92; N, 26.91.

Further elution gave 100 mg of the starting amine **1a**.

Still further elution with dichloromethane-methanol (99-1% v/v) gave 2-(*o*-aminophenyl)imidazole (**7**) as a white powder (100 mg, 21%) mp 135-137° (Lit [3] 128-130°); ms: 159 ($M^{+\cdot}$, 100%), 158 ($M^{+\cdot}-1$, 12), 131 (M^+-28, 50), 118 (9), 104 (22), 91 (7), 77 (10).

Imidazo[1,2-*c*]benzo[*e*][1,2,3]triazine (**6**).

Five hundred mg of **3** (2.96 mmoles) in 4 ml of acetic acid was treated with 1 g of sodium nitrite (14.5 mmoles) in 4 ml of water. The mixture was stirred at 20° for 2 hours. The solution was filtered, the solid was suspended in water and made alkaline with sodium carbonate. The solution was extracted with methylene chloride. Evaporation gave 200 mg of **6** as imidazo[1,2-*c*]benzo[*e*][1,2,3]triazine, mp 111-113°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.66 (d, J = 1.5 Hz, H2), 7.78 (td, H8), 7.87 (td, H9), 8.25 (d, H3), 8.33 (dd, J = 9 Hz, H7) and 8.46 (dd, J = 9 Hz, H10); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 115.41 (C3), 117.30 (C10a), 121.29 (C10), 129.74 (C7), 130.24 (C8), 132.08 (C2), 132.79 (C10b), 133.95 (C9) and 138.33 (C6a), ms: (EI) 170 ($M^{+\cdot}$, 15%), 142 ($M-N_2$, 100), 115 (58), 102 (46), 88 (26), 76 (10), 75 (512), 62 (22).

Anal. Calcd. for $C_9H_6N_4$: C, 63.53, H, 3.53; N, 32.94. Found: C, 63.38; H, 3.64; N, 32.98.

2-Bromoimidazo[1,2-*c*]quinazoline (**7**) and 2,3-Dibromoimidazo-[1,2-*c*]quinazoline (**8**).

Method A.

To 3 g of **3** (0.017 mole) in 25 ml of acetic acid was added 1.5 ml (4.77 g, 0.030 mole) of bromine. The mixture was stirred at 20° for 30 minutes and then basified by sodium carbonate. The mixture was extracted with methylene chloride (3 × 200 ml). The organic layers were dried with calcium chloride. After concentration the residue was chromatographed on neutral alumina eluted with dichloromethane to give the 2,3-dibromoimidazo[1,2-*c*]quinazoline (**8**), 2 g (35%) as a white powder which became pink in light, mp 207-209°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.69 (td, H8), 7.75 (td, H9), 7.98 (dd, H7), 8.48 (dd, H10) and 8.77 (s, H5); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 96.04 (C3), 117.88 (C10a), 122.37 (C10), 123.72 (C2), 128.77 (C7), 129.45 (C9), 131.05 (C8), 134.51 (C5), 140.84 (C6a), 143.73 (C10b); ms: (EI) 329 (M+4, 51%), 327 (M+2, 100), 325 ($M^{+\cdot}$, 50), 248 ($M^+-{}^{79}Br$, 11), 246 ($M^+-{}^{81}Br$, 10), 221 ($M^+-{}^{79}Br-HCN$, 13), 219 ($M^+-{}^{81}Br-HCN$, 14), 196 (2), 194 (2), 167 (28), 149 (39), 129 (27), 114 (13), 102 (17), 71 (20).

Anal. Calcd. for $C_{10}H_5Br_2N_3$: C, 36.70; H, 1.53; Br, 48.93; N, 12.84. Found: C, 36.91; H, 1.50; Br, 48.79; N, 12.80.

Further elution gave 1 g (23%) of 2-bromoimidazo[1,2-*c*]quinazoline (**7**) mp 216-218°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.65 (s, H3), 7.66 (td, H8), 7.72 (td, H9), 7.93 (dd, H7), 8.49 (dd, H10) and 8.81 (s, H5); ^{13}C nmr (deuteriochloroform): 75 MHz δ 111.27 (C3), 118.48 (C10a), 122.14 (C2), 122.79 (C10), 128.59 (C7), 129.18 (C9), 130.71 (C8), 135.41 (C5), 140.81 (C6a) and 142.95 (C10b); ms: (EI) 249 (M + 2, 96%), 247 ($M^{+\cdot}$, 100), 168 (M^+-Br, 59), 141 (66), 129 (12), 114 (30), 102 (19).

Anal. Calcd. for $C_{10}H_6BrN_3$: C, 48.39; H, 2.42; Br, 32.25; N, 16.94. Found: C, 48.30; H, 2.49; Br, 32.38; N, 16.83.

Method B.

Five hundred mg of imidazol[1,2-*c*]quinazoline (**3**) (2.96 mmoles) was suspended in 25 ml of carbon tetrachloride. Nine Hundred mg of *N*-bromosuccinimide was added and the mixture was refluxed for 10 minutes. The insoluble succinimide was removed by filtration and the resulting orange solution was evaporated to dryness. The residue was purified by chromatography on alumina. Elution with methylene chloride gave first 2,3-dibromoimidazo[1,2-*c*]quinazoline (**8**), 200 mg (21%). Further elution gave 2-bromoimidazo[1,2-*c*]quinazoline (**7**), 250 mg (35%). These compounds were identical to those obtained by method A.

3-Nitroso-2-(4′-methoxyphenyl)imidazo[1,2*c*]quinazoline (**10**).

Five hundred mg of **2b** (1.82 mmoles) in 4 ml of acetic acid was treated in the same manner for 20 minutes. The solution was filtered off, the residue suspended in water, made alkaline and extracted with dichloromethane and evaporated to dryness. 3-Nitroso-2-(4′-methoxyphenyl)imidazo[1,2-*c*]quinazoline (**10**) was purified by recrystallisation in methylene chloride to give green plates (300 mg, 54%): mp 245-247°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 3.87 (s, OCH_3), 7.15 (d, J = 9.5 Hz, H3′, 5′), 8.30 (m, H7, 8, 9), 8.92 (m, H10, 2′, 6′), 10.02 (s, H5); ms: (EI) 304 ($M^{+\cdot}$, 100%), 303 (M^+-H, 15), 287 (M^+-OH, 68), 274 (M^+-NO, 31), 261 (38), 231 (59), 146 (14), 129 (38), 119 (23), 102 (55), 90 (12), 77 (11), 76 (34), 75 (28).

Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.95; N, 18.42. Found: C, 66.97; H, 3.83; N, 18.60.

Further elution with (dichloromethane-methanol): 2% gave 100 mg of **11** as *N*-(4-quinazolinyl)-4′-methoxybenzimidoyl cyanide as orange plates (19%), mp >260°; ir (potassium bromide): cm^{-1}, 2232 (CN), 1672 (C=N−C); ^{1}H nmr (perdeuteriomethanol): 60 MHz, δ 3.86 (s, OCH_3), 7.23 (d, 2H), 7.47 (m, 2H), 8.50 (s, 1H), 9.07 (d, 2H); ms: (EI) 288 ($M^{+\cdot}$, 34%), 287 (41), 273 (21), 133 (16), 77 (8), 76 (9).

2-(3′,5′-Dinitro-4′-methoxyphenyl)imidazo[1,2-*c*]quinazoline (**12**).

Five Hundred mg of **2** (1.82 mmoles) was treated in the same manner. When the acidic mixture was poured into water, a precipitate was formed. After filtration, the solid was suspended in water and made alkaline with sodium carbonate. After extraction, drying, and evaporation the residue was chromatographed on neutral alumina. Elution with dichloromethane-methanol, 0.5% gave 440 mg of **12** as 2-(3′,5′-dinitro-4′-methoxyphenyl)imidazo[1,2-*c*]quinazoline (66%) as yellow plates, mp 251-253°; ^{1}H nmr, 300 MHz, δ 4.13 (s, OCH_3), 7.73 (td, H8), 7.78 (td, H9), 7.99

(dd, H7), 8.03 (s, H3), 8.61 (dd, H10), 8.68 (s, H2', 6'), 8.92 (s, H5); ms: (EI) 365 ($M^{+\cdot}$, 100%), 350 ($M^+ - CH_3$, 3), 335 ($M^+ - NO$, 8), 334 ($M^+ - OCH_3$, 2), 289 (13), 244 (10), 142 (2), 133 (11), 102 (19), 90 (11), 76 (12).

Anal. Calcd. for $C_{17}H_{11}N_5O_5$: C, 54.40; H, 2.93; N, 18.67. Found: C, 54.22; H, 3.05; N, 18.55.

The same technique with 2 hours of stirring at 0° gave the same product in an equivalent amount.

3-Bromo-2-(4'-methoxyphenyl)imidazo[1,2-*c*]quinazoline (**13**).

To 500 mg of (**2b**) (1.82 mmoles) was in 4 ml of acetic acid add 0.15 ml of bromine (477 mg, 2.98 mmoles). The mixture was stirred for 30 minutes at room temperature, and then filtered. The solid was taken up in water and the solution made basic with sodium carbonate, extracted with methylene chloride, dried and evaporated *in vacuo*. The residue was chromatographed on neutral alumina eluted with methylene chloride to give 460 mg of 3-bromo-2-(4'-methoxyphenyl)imidazo[1,2-*c*]quinazoline as a white powder (72%) mp 157-159°; ^1H nmr (perdeuteriomethanol): 300 MHz, δ 3.89 (s, OCH_3), 7.03 (d, J = 9 Hz, H3', 5'), 7.66 (td, H8), 7.72 (td, H9), 7.97 (dd, H7), 8.11 (d, H2', 6'), 8.60 (dd, H10), 8.88 (s, H5).

Anal. Calcd. for $C_{17}H_{12}BrN_3O$: C, 57.63; H, 3.39; Br, 22.60; N, 11.86. Found: C, 57.72; H, 3.46; Br, 22.42; N, 11.72.

5-Methylimidazo[1,2-*c*]quinazoline (**15**) and 5,6-Dihydro-5,5-dimethylimidazo[1,2-*c*]quinazoline (**14**).

To a solution of 338 mg of imidazo[1,2-*c*]quinazoline (**3**) (2 mmoles) and 2.22 g of ferrous sulfate heptahydrate (8 mmoles) in 75 ml of 1*N* sulfuric acid, 1 g of *t*-butyl hydroperoxide (70% in water) was added dropwise at room temperature during 5 minutes with stirring. After 30 minutes standing at this temperature, aqueous barium hydroxide solution was added to adjust the *p*H of the mixture above 10. The alkaline solution was filtered through Celite, extracted with methylene chloride and evaporated *in vacuo*. The residue was chromatographed on alumina. Elution with methylene chloride gave 100 mg of 5-methylimidazo[1,2-*c*]quinazoline as white platelets (27%), mp 118-120° (Lit [4] 124-126°); ^1H nmr (deuteriochloroform): 60 MHz, δ 2.87 (s, CH_3), 7.77 (m, H2, 3, 7, 8, 9), 8.57 (m, H10); ms: (EI) 183 ($M^{+\cdot}$, 100%), 182 ($M^+ - 1$, 69), 157 ($M^+ - HCN$, 10), 141 (3), 129 (9), 102 (18), 76 (5).

Further elution gave the starting imidazo[1,2-*c*]quinazoline (**3**) (180 mg).

Still further elution gave 5,6-dihydro-5,5-dimethylimidazo-[1,2-*c*]quinazoline (**14**) as white plates, 20 mg (5%) mp 189-191°; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.71 (s, 6H, $(CH_3)_2$), 4.22 (m, 1H, NH), 7.01 (m, 4H), and 7.98 (dd, 1H); ms: (EI) 199 ($M^{+\cdot}$, 100%), 198 ($M^+ - 1$, 70), 184 ($M^+ - CH_3$, 10).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.36; H, 6.53; N, 21.11. Found: C, 72.52; H, 6.41; N, 21.07.

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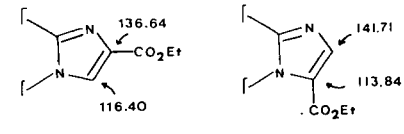
[13] The structure of ethyl imidazo[1,2-*a*]pyrimidine-2 and 3-carboxylate published by Abignente [14] were assigned on the bases of 2D heteronuclear shift correlation experiment ($^1H - ^{13}C$ HETCOR) on 2-substituted compound.



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