New Entry to Indazolo[2,3-*a*]quinazolines by Revision of the Reported Structure of an Indolo[1,2-*b*]indazole Derivative

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The reported structure of an indolo[1,2-*b*]indazole derivative is revised to a indazolo[2,3-*a*]quinazoline derivative based on detailed NMR analyses and chemical transformation.

Key words indazolo[2,3-*a*]quinazoline; revision; indolo[1,2-*b*]indazole; NMR spectrum; chemical transformation

We have been studying the chemistry and biological activities of pyrazolo[1,5-*a*]indole derivatives in search of compounds of potential medicinal value.[1] As a part of this effort we needed to prepare indolo[1,2-*b*]indazoles, the [*b*]benzo analogue of pyrazolo[1,5-*a*]indole. Among many possible isomers, we are especially interested in 6*H* and 11*H* isomers, **1** and **2**, in relation to 1*H*- and 4*H*-pyrazolo[1,5-*a*]indoles.[1a,d] There have been a few reports concerning the synthesis of indolo[1,2-*b*]indazoles.[2] Among them, we were attracted by the method of Gale and Wilshire,[2a] who synthesized the indolo[1,2-*b*]indazole derivative **3** by acid treatment of the nitrile **4**, a substitution product of 2-fluoro-5-nitrobenzonitrile, with indazole (Chart 1).[3] When we repeated this reaction, the reported product **3** was obtained in good yield. Assignment of the structure **3** was based on MS (M^+ at *m/z*: 264) and IR (1635 cm^{-1} for C=NH) spectra, together with elemental analysis. They also measured the ^{1}H-NMR spectrum in trifluoroacetic acid (**3** was insoluble in ordinary solvents) but the chemical shifts without coupling constants are not conclusive in supporting the proposed structure. When we had measured the spectra of this compound and carried out a few reactions, the following questions arose. 1) No NH absorption band was detected in the IR spectrum. 2) No reaction (recovery of the starting material) took place in acetylation (refluxing with a complex of acetic anhydride and pyridine), acid hydrolysis (refluxing in 48% HBr solution) and reduction (sodium borohydride in methanol) procedures. Since the reported compound **3** has poor solubility in ordinary NMR solvents, its nitro group was reduced catalytically with 5% palladium on charcoal in a hydrogen atmosphere. The amino product (60% yield) has better solubility, so structural analysis was carried out spectroscopically. In the IR spectrum the absorptions of NH_2 (3339, 3231 cm^{-1}) and C=N (1645 cm^{-1}) groups were detected. In the ^{1}H-NMR spectrum in dimethyl sulfoxide-d_6 (DMSO-d_6), a singlet signal appeared at δ 9.02, which is assignable to C=N–H. However, when the ^{13}C-NMR spectrum was measured, this proton was found to be attached to carbon (δ 146.3 ppm). Since the signal at δ 9.02 is too low-filed for an aromatic proton at C-1 in the structure **3**, we thought that the C=NH unit should be changed to a CH=N-unit and included in the ring. As a skeletal isomer of the reported structure **3**, two skeletons were considered for indolo[1,2-*b*]indazole, *i.e.*, indazolo[2,3-*a*]quinazoline and indazolo[2,3-*a*]quinoxaline, of which the latter was tentatively excluded from a mechanistic point of view. Accordingly the structure **3** was revised to **5a** and the amino product obtained above was assigned the structure **5b**. When this structure **5b** was used to rationalize the NMR signals, the following inconsistency

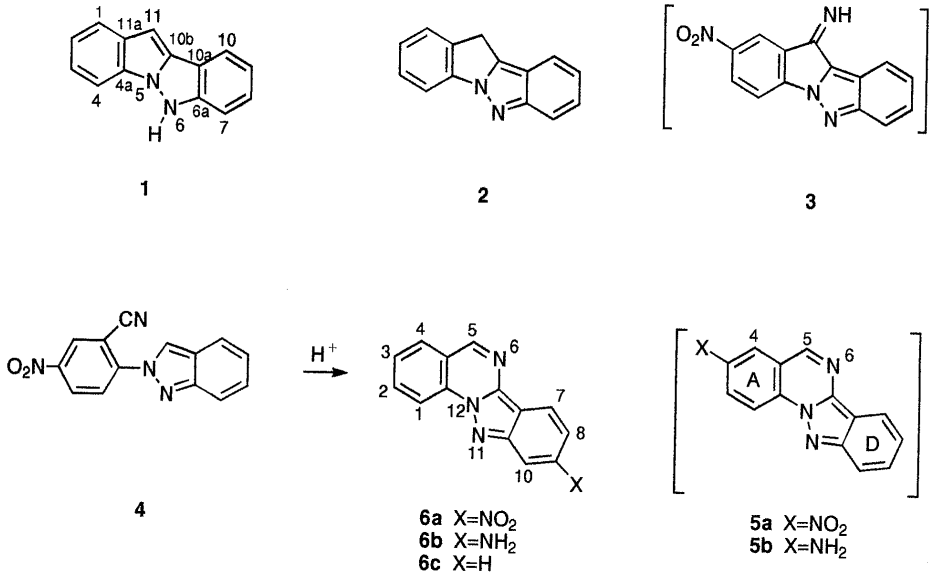

Chart 1

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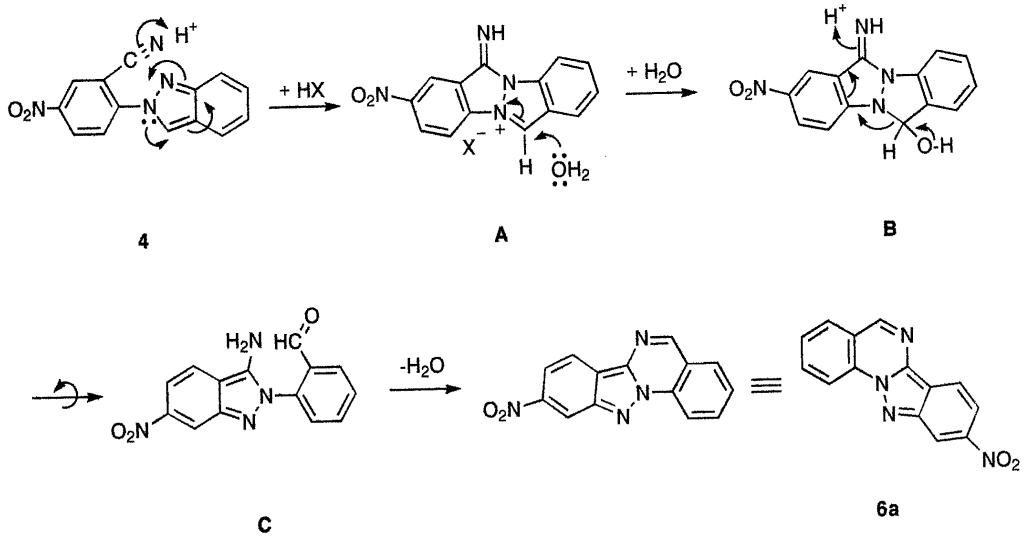

Chart 2

was found. Although nuclear Overhauser effect (NOE) was observed between 5-H (δ 9.01, s) and 4-H (δ 8.26, d, $J=8.8$ Hz), the coupling constant for 4-H is too big for a *meta* coupling constant (*ca.* 2 Hz) based on the structure **5b**. To explain this big coupling constant there should be a proton adjacent to 4-H, and the amino group on ring A should be moved to ring D. As the position of the amino group on the D ring, either C-8 or C-9 was considered but no definitive conclusion could be reached from the NMR spectra. However, the position C-9, *i.e.*, the structure **6b**, was selected from a mechanistic consideration (Chart 2). Thus, the structure **5b** was revised again to **6b**. Based on the structure **6b**, all the NMR signals observed for the amino product could be reasonably assigned (see Experimental). Support for the skeleton of the structure **6b** was obtained by chemical transformation. The amino group of **6b** was diazotized with isoamyl nitrite and removed by refluxing the resulting diazonium salt in tetrahydrofuran.[4] The greenish-yellow product thus obtained (37% yield) was identified as indazolo[2,3-*a*]quinazoline **6c**[5] on the basis of melting point (free base and its picrate) and ^{1}H-NMR spectrum. The NOE was also detected in **6c** between 5-H (δ 9.02, s) and 4-H (δ 8.07, dd, $J=8.1$, 1.0 Hz). Splitting patterns of all aromatic protons, including 4-H, support the structure **6b**.

The proposed reaction mechanism for the formation of **6a** from **4** is summarized in Chart 2. In this mechanism the protonated cyano group is attacked nucleophilically by indazole nitrogen (N-1) to give the quadracyclic hydrazine derivative A as the first stage of reaction.[6] The C-3 in the indazolium unit of A is most electron-deficient, and thus is attacked by water to give the hemiaminal B. With the assistance of acid, this hemiaminal ring is opened and isomerization of the resulting product to 2*H*-indazole form, together with rotation of the *o*-formylphenyl group, gives the intermediate C. Finally acid-catalyzed intramolecular condensation between the amino and formyl groups in C results in the formation of **6a**.

In conclusion, we have shown that the reported structure **3** is incorrect and its structure is revised to the structure **6a**. This finding provides a new entry to indazolo[2,3-*a*]quinazoline derivatives starting with indazoles.

Experimental[7]

3-Aminoindazolo[2,3-*a*]quinazoline (6b) The nitro compound **6a** (0.402 g, 1.52 mmol) was dissolved in methanol (25 ml) and hydrogenated over 5% Pd–C (0.3 g) under hydrogen (3 atm). The solution was filtered and the filtrate was evaporated to give a red crystalline product (0.334 g, 93.8%), which was recrystallized from dichloromethane–isopropyl ether to afford 0.213 g (59.8%) of **6b**, mp 218.0—221.0 °C. MS *m/z* (rel. int. %): 234 (M^+, 100), 155 (19.8), 141 (19.0), 129 (18.4). IR cm^{-1}: 3339, 3231, 1645, 1617, 1588, 1549 (s), 1298, 1202, 813, 762. ^{1}H-NMR (DMSO-d_6) δ: 5.30 (2H, br s, NH_2), 7.14 (1H, br s, 10-H), 7.15 (1H, dd, $J=7.0$, 2.2Hz, 8-H), 7.69 (1H, d, $J=10.0$ Hz, 7-H), 7.75 (1H, t with small couplings, $J=7.6$ Hz, 3-H), 8.05 (1H, ddd, $J=8.4$, 7.2, 1.2 Hz, 2-H), 8.26 (1H, br d, $J=8.8$ Hz, 4-H), 8.59 (1H, d, $J=8.3$ Hz, 1-H), 9.01 (1H, s, 5-H). NOE's were detected between the following protons in the phase sensitive nuclear Overhauser effect spectroscopy (PNOSY) spectrum: 5-H/4-H, 1-H/8-H, 4-H/3-H and 5-H, 2-H/3-H and 1-H, 7-H/8-H. ^{13}C-NMR δ (DMSO-d_6): 96.5 (d, C-10), 114.9 (d, C-1), 115.9 (s, C-9), 117.4 (d, C-7), 119.7 (s, C-4a), 123.1 (d, C-8), 126.4 (d, C-3), 128.7 (d, C-4), 133.8 (d, C-2), 134.9 (s, C-12a), 137.1 (s, C-10a), 143.7 (s, C-6a), 144.5 (s, C-6b), 146.3 (d, C-5).

Deamination of 6b A solution of **6b** (234 mg, 1 mmol) in dry tetrahydrofuran (THF) (12 ml) was slowly added to a solution of isoamyl nitrite (140 mg, 0.16 ml, 1.2 mmol) in dry THF (10 ml) under dry nitrogen for 1 h. The resulting solution was refluxed for 10 h. The color of the solution changed from red to dark brown during this period. The solution was evaporated and the residue (0.33 g) was chromatographed (silica gel 15 g, hexane–ethyl acetate, 3 : 1) to give, together with recovered **6b** (0.16 g), the indazolo[2,3-*a*]quinazoline **6c** (81 mg, 37%), mp 170.0—171.0 °C (EtOH) (lit.[5] 170—171 °C). IR cm^{-1}: 1642, 1617, 1549, 1301, 1211, 736, 758, 744. MS *m/z* (rel. int. %): 219 (M^+, 100), 190 (20.3), 189 (8), 164 (15.6), 163 (4), 140 (4.6), 129 (6.9), 115 (6.6), 114 (6.4), 109 (19.6), 102 (13.9), 88 (6.7). ^{1}H-NMR δ: 7.34 (1H, ddd, $J=8.4$, 8.3, 0.9 Hz, 8-H), 7.60 (1H, ddd, $J=8.8$, 8.4, 1.3 Hz, 9-H), 7.69 (1H, ddd, $J=8.5$, 8.1, 0.9 Hz, 3-H), 7.94 (1H, dt-like, $J=8.8$ Hz, 10-H), 8.00 (1H, ddd, $J=8.5$, 8.4, 1.0 Hz, 2-H), 8.07 (1H, dd, $J=8.1$, 1.0 Hz, 4-H), 8.30 (1H, dt-like, $J=8.3$ Hz, 7-H), 8.81 (1H, dd, $J=8.4$, 0.9 Hz, 1-H), 9.02 (1H, s, 5-H). ^{13}C-NMR δ: 115.4 (C-6b), 116.3 (C-1), 116.9 (C-10), 120.3 (C-7+C-4a), 121.9 (C-8), 126.7 (C-3), 128.3 (C-4), 128.9 (C-9), 133.9 (C-2), 135.6 (C-12a), 139.9 (C-6a), 148.3 (C-5), 149.9 (C-10a). The picrate was formed by treating the free base with saturated picric acid in ethanol, mp 120—123 °C (EtOH) (lit.[5] 120—122 °C).

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References and Notes

1) *a*) Shen J.-K., Katayama H., *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1871; *b*) *Idem*, *Chem. Pharm. Bull.*, **42**, 214 (1994); *c*) *Idem*, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2087; *d*) Katayama H., Sakurada M., Herath W. H. H., Takatsu N., Shen J.-K., *Chem. Pharm. Bull.*, **40**, 2267 (1992).

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5) Hill D. T., Stanley K. G., Libsch S. S., Loev B., *J. Heterocycl. Chem.*, **13**, 1325 (1976).
6) N-1 of 2-alkylated indazoles has relatively strong nucleophilicity, *e.g.*, ready alkylation with alkyl halide (hard electrophile): "The Chemistry of Heterocyclic Compounds," Vol. 23, ed. by Weissberger A., Interscience, N.Y., 1967, pp. 289—382. But nucleophilic attack at a soft electrophile, such as the cyano group (assisted by acid in our case) by N-1 of 2-alkyl indazoles has no precedent to our best knowledge.
7) For general directions see, ref. 1*b*.