REACTION OF 2-BROMO-2,3-DIHYDRO-1H-PYRAZOLO[1,2-a]INDAZOLIUM BROMIDES WITH ALKALINE SOLUTION

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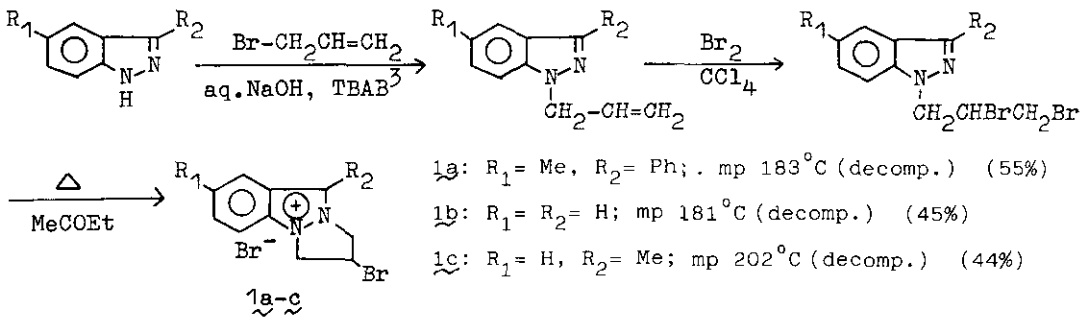
Abstract ——Treatment of 2-bromo-2,3-dihydro-1H-pyrazolo[1,2-a]-indazolium bromides (1a-c) with alkaline solution initially affords 9H-pyrazolo[1,2-a]indazolium bromides (2a-c), which are further convertible by dehydrobromination into pyrazolo-[1,2-a]indazoles (3a-c). The 9-position of 3 is susceptible to attack by oxygen and acetyl cation.

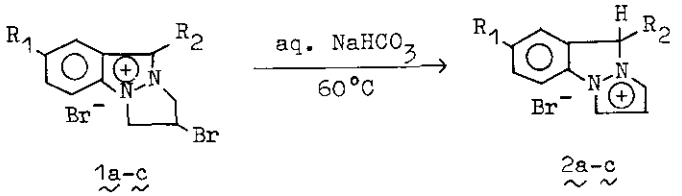
Previously, we reported the synthesis of 2,3-dihydro-1H-pyrazolo[1,2-a]indazolium halides and their bronchodilating activities.[1] In connection with this work, we were interested in pyrazolo[1,2-a]indazoles, a new benzodiazapentalene ring system, and investigated their synthesis by the reaction of 2-bromo-2,3-dihydro-1H-pyrazolo[1,2-a]indazolium bromides (1a-c) with alkaline solutions. The required starting materials 1a-c were prepared in 44-55% overall yields by the following route involving allylation of indazoles, bromination and thermal cyclization.[2]



1a-c

1a: R_1 = Me, R_2 = Ph; . mp 183°C (decomp.) (55%)
1b: R_1 = R_2 = H; mp 181°C (decomp.) (45%)
1c: R_1 = H, R_2 = Me; mp 202°C (decomp.) (44%)

Treatment of 1c with sodium hydrogencarbonate solution at 60°C for 4 h afforded 9-methyl-9H-pyrazolo[1,2-a]indazolium bromide (2c), colorless crystals, mp 206°C (H_2O), in 56% yield. The structure assignment of 2c was based on the satisfactory elemental analysis ($C_{11}H_{11}N_2Br$), the mass spectrum [m/z: 170 (M^+-HBr)], and the nmr spectrum [($CDCl_3$-DMSO-d_6)δ: 2.02 (3H, d, CH_3), 6.40 (1H, q, H_9), 7.10 (1H, t, H_2), 7.55-7.90 (3H, m, Ar-H), 8.55-8.65 (1H, m, Ar-H), 9.32 (1H, d, H_1 or H_3), 9.75 (1H, d, H_1 or H_3)]. In a similar manner, 2a (mp 238°C, 63%) and 2b (mp 223°C, 74%) were obtained from 1a and 1b, respectively. The 9H-pyrazolo[1,2-a]indazolium structure was further established by the X-ray diffraction study of 2a (Fig.).



1a-c 2a-c

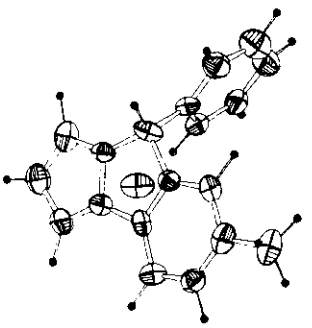
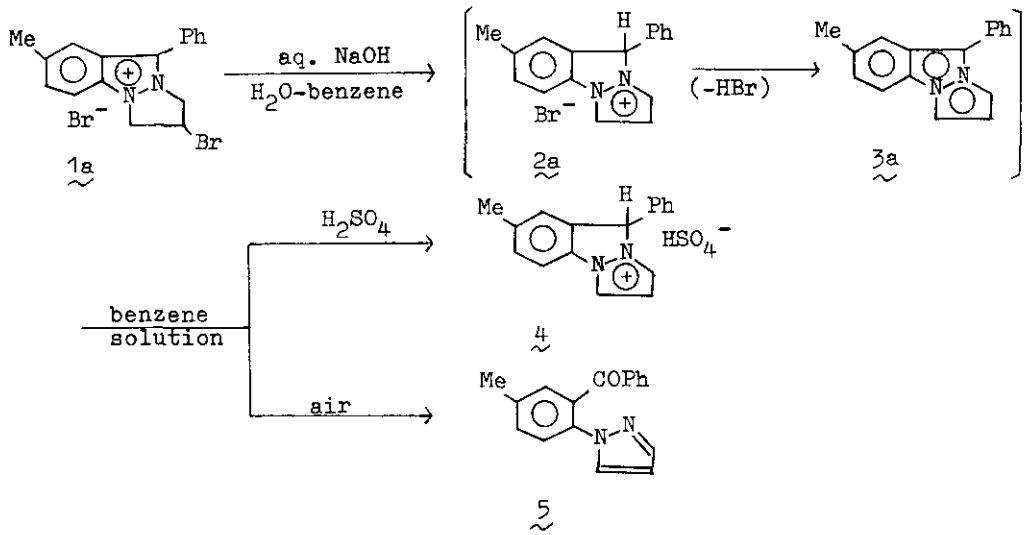
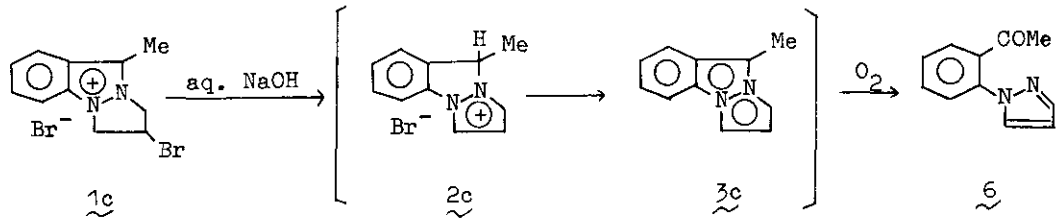


Fig. ORTEP drawing of 2a

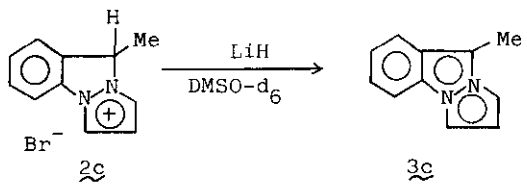
Subsequently the behavior of 1 toward sodium hydroxide solution was explored. A 10% sodium hydroxide solution was added dropwise to an ice-cooled mixture of an aqueous solution of 1a and benzene under stirring in a stream of nitrogen. After 20 min, the benzene layer was separated and treated with conc. sulfuric acid followed by chromatography on HP-20 to give 7-methyl-9-phenyl-9H-pyrazolo[1,2-a]-indazolium hydrosulfate (4)[4] in 25% yield. When the benzene solution obtained from another run was exposed to air, 2-(1-pyrazolyl)-5-methylbenzophenone (5), mp 97-98°C (hexane), was produced in 30% yield. The structure of 5 was confirmed by the satisfactory elemental analysis ($C_{17}H_{14}N_2O$), the mass spectrum [m/z: 262 (M^+)], and the ir spectrum [νcm^{-1}: 1680 (C=O)]. These results may be illustrated by the intermediacy of 7-methyl-9-phenyl-pyrazolo[1,2-a]indazole (3a). The initially formed 9H-pyrazolo[1,2-a]indazolium bromide (2a) converts by dehydrobromination to 3a which transfers from the aqueous layer to the benzene phase. Treatment with sulfuric acid causes protonation at the 9-position of 3a to give 4, and the formation of 5 arises from air oxidation at the same position and the ring rupture.



When an aqueous solution of 9-methylindazolium bromide 1c was treated with 10% sodium hydroxide solution under ice-cooling in a stream of nitrogen, the immediate disappearance of 1c and the formation of the corresponding 9H-pyrazolo[1,2-a]-indazolium bromide (2c) were noticed on thin-layer chromatogram. Upon exposure of this alkaline solution to the atmosphere at room temperature for 2 days 2-(1-pyrazolyl)-acetophenone (6) was obtained as an oil in 46% yield; ms [m/z: 186 (M^+)], ir [νcm^{-1}: 1680 (C=O)]. The formation of 6 can be similarly illustrated by the intermediacy of 9-methylpyrazolo[1,2-a]indazole (3c).

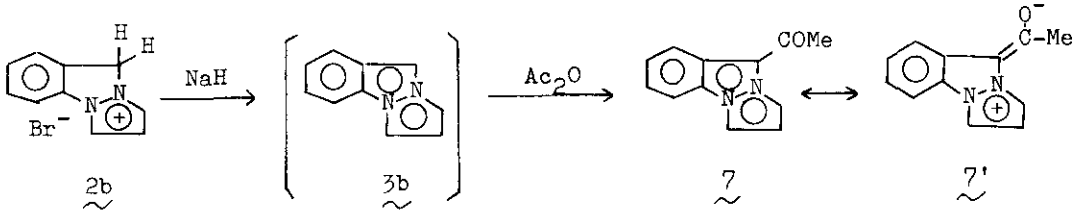


The existence of 3c was supported by the nmr studies.[2a] Compound 2c was dissolved in DMSO-d_6 in a nmr tube and treated with an excess of lithium hydride under nitrogen atmosphere. The 9-methyl signal appeared as a singlet at δ2.45 and the aromatic protons at δ6.5-8.0 as a multiplet. Although the signals of the pyrazole protons of 3c could not be clearly characterized owing to overlapping with other aromatic proton signals, they were shifted upfield as



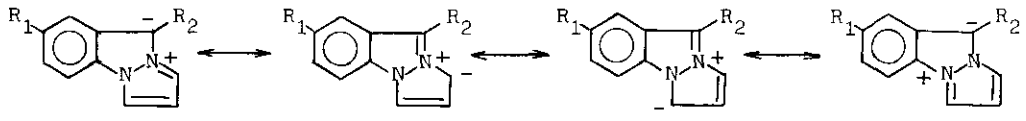
compared with those of 2c. This observation indicates that the positively charged pyrazole ring of 2c changed to a neutral ring system.

Treatment of 2b with sodium hydride and acetic anhydride in DMF-DMSO gave 9-acetylpyrazolo[1,2-a]indazole (7) though in a low yield of 7%; mp 140°C[5], ms [m/z: 198 (M^+), 155 (M^+-Ac)], nmr [($CDCl_3$) δ: 2.57 (3H, s, CH_3), 6.83 (1H, t, H_2), 7.1-7.8 (4H, m, $H_{5,6,7,8}$), 7.81 (1H, d, H_1 or H_3), 8.86 (1H, d, H_1 or H_3)], ir [νcm^{-1}: 1540 (C=O)]. While the nmr spectrum shows two one-proton doublets due to H_1 and H_3, and a one-proton triplet due to H_2, its signal pattern is similar to that of 2b rather than that of 3c. This observation and the strong carbonyl band at 1540 cm^{-1} in the ir spectrum suggest the great contribution of the ionic canonical formula (7').[6]



2b 3b 7 7'

Thus, the reaction of 2-bromo-2,3-dihydro-1H-pyrazolo[1,2-a]indazolium bromides (1a-c) with alkaline solution was found to proceed by the following two-step course. The first step is the formation of the 9H-pyrazolo[1,2-a]indazolium bromides (2a-c) by dehydrobromination and a proton shift; the second one is aromatization of 2a-c to the pyrazolo[1,2-a]indazoles (3a-c) by further dehydrobromination. It is very significant that 2a-c were isolated as a fairly stable species, and the direct transformation of 1a-c to 3a-c seems unlikely in the above-mentioned cases. Apparently the electron density at the 9-position is fairly larger than that at the 1- or 3-position in the benzodiazapentalene system 3. This characteristic property may well be explicable in terms of larger participation of structures having a negative charge at the 9-position (I and IV) in the resonance system than 1- or 3-negatively charged structure (II or III) owing to the conjunction of a benzene ring.[7]



I II III IV

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1. a) Y. Fujimura, S. Tanaka, I. Matsunaga, Y. Shiraki, Y. Ikeda, T. Yamazaki, Y. Ohba, S. Hata, M. Shindo, and K. Sakai, European patent No. 0023633 (1981).
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2. a) T.W.G. Solomons and C.F. Voigt, J. Am. Chem. Soc., 1966, 88, 1992.
   b) S. Trofimenko, J. Am. Chem. Soc., 1966, 88, 5588.
3. Tetrabutylammonium bromide (a phase transfer catalyst).
4. Compound 4 is hygroscopic and decomposes at 170°C. Treatment of 4 with silver nitrate gave no precipitate.
5. Compound 7 is unstable and begins to decompose at ca. 70°C and decomposes completely at 140°C.
6. T.W.G. Solomons, F.W. Fowler, and J. Calderazzo, J. Am. Chem. Soc., 1965, 87, 528.
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