Synthesis of 1-Substituted 3-(Dialkylaminoalkoxy)-4,5,6,7-tetrahydro-1*H*-indazoles

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Synopsis. 4,5,6,7-Tetrahydro-3-indazolone was prepared by catalytic hydrogenation of 3-indazolone, and its reaction with dialkylaminoalkyl chloride was studied. In addition, a number of 1-substituted 3-(dialkylaminoalkoxy)-4,5,6,7-tetrahydro-1*H*-indazoles were prepared.

Indazole[1] nucleus is of high therapeutic interest and benzydamine[2] represents an antiinflammatory drug with this heterocyclic nucleus. Barbaz *et al.*[3] reported the synthesis of 1-substituted 3-hydroxy-4,5,6,7-tetrahydro-1*H*-indazoles (**8**) by cyclization of *N*-substituted 2-chlorocyclohexene-1-carbohydrazides and the 3-*O*-alkylation of **8** to give 1-substituted 3-(dialkylaminoalkoxy)-4,5,6,7-tetrahydro-1*H*-indazoles (**7**). In this paper, we describe a new synthesis of a series of 3-(dialkylaminoalkoxy)-4,5,6,7-tetrahydro-1*H*-indazoles (**3**) and its 1-substituted derivatives (**7**). We have prepared 4,5,6,7-tetrahydro-3-indazolone (**2**) in good yield by catalytic hydrogenation of 3-indazolone (**1**) with palladium catalyst and identified it by comparison with an authentic specimen prepared by the procedure of Dieckmann.[4]

As to alkylation of **2**, Alt and Chupp[5] reported that the alkylation of **2** with alkyl halides in aqueous ethanolic sodium hydroxide gave 1-substituted derivatives (**8**). We have found that, when the reaction of **2** with 3-(dimethylamino)propyl chloride is carried out in a nonaqueous medium, a 3-*O*-monosubstituted derivative, namely, 3-[3-(dimethylamino)propoxy]-4,5,6,7-tetrahydro-1*H*-indazole (**3a**) is mainly produced in 57% yield. A minor product in this reaction was 1,3-*O*-disubstituted derivative, namely, 3-[3-(dimethylamino)propoxy]-1-[3-(dimethylamino)propyl]-4,5,6,7-tetrahydro-1*H*-indazole (**5**). Similar treatment of **2** with 2-(diethylamino)ethyl chloride in dioxane gave 3-[2-(diethylamino)ethoxy]-4,5,6,7-tetrahydro-1*H*-indazole (**3b**). The structures of **3a** and **3b** were deduced mainly from the NMR spectra, which exhibited signals at δ 4.10—4.12 (t, 3-O-C$\underline{H}_2$-CH$_2$-), indicating the 3-*O*-substitution.

As an alternative possibility to the above mentioned synthesis of 3-*O*-substituted 4,5,6,7-tetrahydro-1*H*-indazolones (**3**), we studied the catalytic hydrogenation of 3-(dialkylaminoalkoxy)-1*H*-indazoles (**4**)[6] previously reported by us, and obtained **3a** from 3-[3-(dimethylamino)propoxy]-1*H*-indazole (**4a**) in 92% yield. Compound **3b** was further obtained by the similar catalytic hydrogenation of 3-[2-(diethylamino)ethoxy]-1*H*-indazole (**4b**).[6] The above mentioned compound **5** was also obtained by catalytic hydrogenation of 3-[3-(dimethylamino)propoxy]-1-[3-(dimethylamino)-propyl]-1*H*-indazole (**6**).[6]

Thus, the 3-*O*-substituted 4,5,6,7-tetrahydro-1*H*-indazolones (**3**) have been synthesized by the route (**1**)→(**2**)→(**3**) and another route (**4**)→(**3**). In addition, the 3-*O*-substituted compounds (**3**) were led to 1,3-*O*-disubstituted 4,5,6,7-tetrahydro-1*H*-indazolones (**7**) by reaction of the sodium salt of **3** with alkyl halides or other halides in liquid ammonia or hexamethylphosphoric triamide. The structures of **7** were confirmed by their NMR, IR, and UV spectra.

Experimental

4,5,6,7-Tetrahydro-3-indazolone (2). A solution of 3-indazolone (**1**,[7] 0.89 g) in acetic acid (30 ml) was hydrogenated in the presence of Pd–carbon (Pd 5%) (2.67 g) under hydrogen atmosphere at 50 °C for about 7 h. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give **2**, crystals, mp 289.5—291.5 °C (0.79 g, 86%). Recrystallization from methanol gave mp 293.5—295.0 °C. UV$_{max}$(C_2H_5OH): 250 nm (ε 6350). This material was identified by the determination of mixed melting point with an authentic specimen.[4]

3-[3-(Dimethylamino)propoxy]-4,5,6,7-tetrahydro-1H-indazole (3a). By Reaction of 2 with 3-(Dimethylamino)propyl Chloride: A sample of **2** (5.53 g) was dissolved in an aqueous 1 M sodium hydroxide (40 ml) with stirring. The solution was evaporated under reduced pressure to give a solid of sodium salt, which was further dried in an oven. The salt was powdered and suspended in dry dioxane (134 ml). A solution of 3-(dimethylamino)propyl chloride (5.11 g) in dry dioxane (66 ml) was added under stirring and refluxing over a 1.5 h period. Refluxing and stirring were further continued for 4.5 h. The reaction mixture was worked up in the usual way to give an oily product (6.65 g), which consisted of two components, **3a** and **5**, as judged by GLC

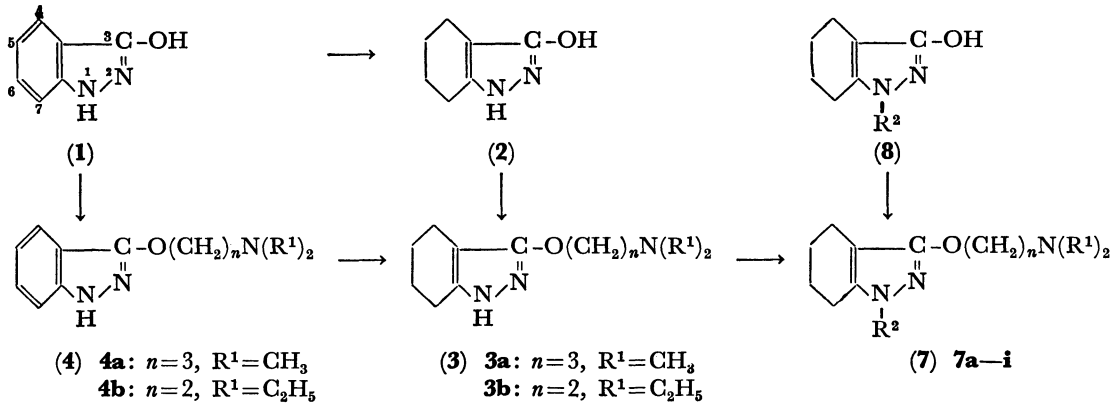

Table 1. 1-Substituted (R^2) 3-[3-(dimethylamino)-propoxy]-4,5,6,7-tetrahydro-1*H*-indazoles (**7c—i**)

No.	R^2	Yield[a] %	Formula[b]	Mp[b] °C	Found[b] (Calcd) (%) C	H	N	Cl
7c	CH_3	30	$C_{13}H_{24}ClN_3O$	158.0—160.0	56.79 (57.03)	8.78 (8.84)	15.40 (15.35)	12.76 (12.95)
7d	C_2H_5	92	$C_{14}H_{26}ClN_3O$	123.0—124.0	58.13 (58.42)	9.03 (9.10)	14.72 (14.60)	12.41 (12.32)
7e	o-$CH_3C_6H_4CO$-	65	$C_{20}H_{28}ClN_3O_2$	174.0—175.0	63.26 (63.56)	7.46 (7.47)	11.18 (11.12)	9.71 (9.38)
7f	m-$CH_3C_6H_4CO$-	51	$C_{20}H_{28}ClN_3O_2 \cdot H_2O$	90.0—91.5	60.97 (60.67)	7.47 (7.64)	10.73 (10.61)	— (8.95)
7g	p-$CH_3C_6H_4CO$-	42	$C_{20}H_{28}ClN_3O_2$	170.0—170.5	63.86 (63.56)	7.43 (7.47)	11.00 (11.12)	9.22 (9.38)
7h	o,o-$(CH_3)_2C_6H_3CO$-	93	$C_{21}H_{30}ClN_3O_2$	179.0—180.0	64.04 (64.35)	7.82 (7.72)	10.63 (10.72)	9.35 (9.05)
7i	p-$CH_3C_6H_4SO_2$-	53	$C_{19}H_{28}ClN_3O_3S$	197.5—199.5	54.91 (55.13)	6.93 (6.82)	9.99 (10.15)	— (8.56)

a) Free base. b) Hydrochloride. $UV_{max}(H_2O)$: **7c**,[b] 229 nm (ε 6820); **7d**,[b] 230 nm (ε 6650).

analysis. Chromatography on silica gel with benzene–diethylamine (9:1) afforded **3a**, an oil, 5.05 g (57%) as main product. $UV_{max}(C_2H_5OH)$: 226 nm (ε 5460). IR (neat): ν_{NH} 3150 and $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 2.19 (6H, s, $-N(C\underline{H}_3)_2$), 4.12 (2H, t, 3-O-$C\underline{H}_2$-CH_2-) and 10.1 (1H, broad, >N$\underline{H}$). Hydrochloride was recrystallized from methanol–ethyl acetate, mp 189.5—191.0 °C. Found: C, 55.53; H, 8.38; N, 16.21; Cl, 13.57%. Calcd for $C_{12}H_{22}ClN_3O$: C, 55.48; H, 8.54; N, 16.18; Cl, 13.63%.

A minor product, 3-[3-(dimethylamino)propoxy]-1-[3-(dimethylamino)propyl]-4,5,6,7-tetrahydro-1*H*-indazole (**5**), (an oil, 1.16 g, 9%) was obtained from the initial eluate with the same solvent. Hydrochloride was recrystallized from methanol–ethyl acetate, mp 194.0—195.0 °C.

*By Catalytic Hydrogenation of 3-[3-(Dimethylamino)propoxy]-1H-indazole (**4a**)*:[6] A solution of **4a** (6.22 g) in acetic acid (160 ml) was hydrogenated in the presence of Adams' catalyst (2.80 g) at room temperature for 12 h. The reaction mixture was worked up in the usual way to give **3a**, an oil, 5.80 g (92%). UV_{max} (C_2H_5OH): 226 nm (ε 5700). IR (neat): ν_{NH} 3160 and $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 4.10 (2H, t, 3-O-$C\underline{H}_2$-CH_2-). Hydrochloride: mp 188.0—189.0 °C.

*3-[3-(Dimethylamino)propoxy]-1-[3-(dimethylamino)propyl]-4,5,6,7-tetrahydro-1H-indazole (**5**)*. Compound **6**[6] (1.00 g) was hydrogenated with Adams' catalyst (1.00 g) at 50 °C for 20 min in acetic acid (15 ml) to give **5** (0.94 g, 93%). UV_{max} (C_2H_5OH): 232 nm (ε 6800). IR (neat): ν_{CH} 2920—2750 and $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 2.12 (6H, s, $1\text{-}(CH_2)_3N(C\underline{H}_3)_2$), 2.16 (6H, s, $3\text{-O-}(CH_2)_3N(C\underline{H}_3)_2$), 3.75 (2H, t, 1-$C\underline{H}_2$-$CH_2$-) and 4.08 (2H, t, 3-O-$C\underline{H}_2$-$CH_2$-). Hydrochloride: mp 194.0—195.0 °C. Found: C, 52.23; H, 8.63; N, 14.02; Cl, 18.27%. Calcd for $C_{17}H_{34}Cl_2N_4O \cdot 1/2H_2O$: C, 52.30; H, 9.03; N, 14.35; Cl, 18.16%.

*3-[2-(Diethylamino)ethoxy]-4,5,6,7-tetrahydro-1H-indazole (**3b**). By Reaction of **2** with 2-(Diethylamino)ethyl Chloride*: A sample of **2** (2.76 g) was caused to react with 2-(diethylamino)-ethyl chloride (2.85 g) in dioxane (100 ml) as described for the preparation of **3a**. The oily product (3.97 g) was chromatographed on silica gel with cyclohexane–diethylamine (9:1) to afford **3b**, 3.10 g (65%). UV_{max} (C_2H_5OH): 225 nm (ε 6170). IR (neat): ν_{NH} 3180 and $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 1.00 (6H, t, J=7 Hz, $-N(CH_2C\underline{H}_3)_2$), 2.55 (4H, q, J=7 Hz, $-N(C\underline{H}_2CH_3)_2$), 2.73 (2H, t, J=6 Hz, 3-O-CH_2-$C\underline{H}_2$-N<) and 4.12 (2H, t, J=6 Hz, 3-O-$C\underline{H}_2$-CH_2-N<). Hydrochloride was recrystallized from methanol–ethyl acetate, mp 130.0—131.0 °C. Found: C, 56.85; H, 8.81; N, 15.34; Cl, 12.67%. Calcd for $C_{13}H_{24}ClN_3O$: C, 57.03; H, 8.84; N, 15.35; Cl, 12.95%.

*By Catalytic Hydrogenation of 3-[2-(Diethylamino)ethoxy]-1H-indazole (**4b**)*:[6] A sample of **4b** (1.17 g) was hydrogenated with Pd–carbon (Pd 5%) (2.00 g) at 60 °C for 10 h in propionic acid (30 ml) to give **3b**, 1.03 g (87%). IR (neat): ν_{NH} 3170 and $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 4.10 (2H, t, J=6 Hz, 3-O-$C\underline{H}_2$-CH_2-N<). Hydrochloride: mp 130.0—131.0 °C.

*1-Benzyl-3-[3-(dimethylamino)propoxy]-4,5,6,7-tetrahydro-1H-indazole (**7a**)*. A mixture of sodium metal (0.61 g) and iron(III) nitrate (20 mg) in liquid ammonia (60 ml) was shaken to precipitate sodium amide. A solution of **3a** (5.14 g) in liquid ammonia (40 ml) was added and kept at room temperature for 1h under shaking. Benzyl chloride (2.92 g) was added and, after shaking, the mixture was stood at room temperature overnight. After evaporation of ammonia, the residue was worked up in the usual way to give an oily product (6.24 g), which was chromatographed on silica gel with cyclohexane–diethylamine (9:1) to afford **7a**, 4.80 g (66%). UV_{max} (C_2H_5OH): 233 nm (ε 9050). IR (neat): $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 4.10 (2H, t, 3-O-$C\underline{H}_2$-CH_2-) and 4.90 (2H, s, 1-$C\underline{H}_2$-C_6H_5). Hydrochloride was recrystallized from 2-propanol–ethyl acetate, mp 149.0—150.0 °C (lit,[3] 143 °C). UV_{max} (H_2O): 232 nm (ε 8590) (lit,[3] 232 nm (ε 8900)). Found: C, 65.19; H, 7.88; N, 12.07; Cl, 10.13%. Calcd for $C_{19}H_{28}ClN_3O$: C, 65.22; H, 8.07; N, 12.00; Cl, 10.13%.

*1-Benzyl-3-[2-(diethylamino)ethoxy]-4,5,6,7-tetrahydro-1H-indazole (**7b**) and Others (**7c—i**)*. To a solution of **3b** (1.60 g) in HMPT (4 ml), sodium hydride (50% in oil) (0.28 g) was added and the solution was heated at 100 °C with stirring for 30 min. After cooling, benzyl chloride (0.74 g) was added and stirred at room temperature for 1 h. The reaction mixture was worked up in the usual way to give **7b**, an oil, 2.04 g (93%). UV_{max} (C_2H_5OH): 232 nm (ε 8810). IR (neat): $\nu_{C=N}$ 1500 cm^{-1}. NMR (CCl_4): δ 4.11 (2H, t, J=6 Hz, 3-O-$C\underline{H}_2$-CH_2-N<) and 4.90 (2H, s, 1-$C\underline{H}_2$-C_6H_5). Citrate was recrystallized from acetone, mp 77.5—81.5 °C. Found: C, 60.28; H, 7.38; N, 8.30%. Calcd for $C_{26}H_{37}N_3O_8$: C, 60.10; H, 7.18; N, 8.09%.

The other compounds (**7c—i**) shown in Table 1 were similarly prepared from **3a** and acid halides or alkyl halides.

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