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POLYAZOLE SYSTEMS BASED ON 3,4-DIHYDROISOQUINOLINE

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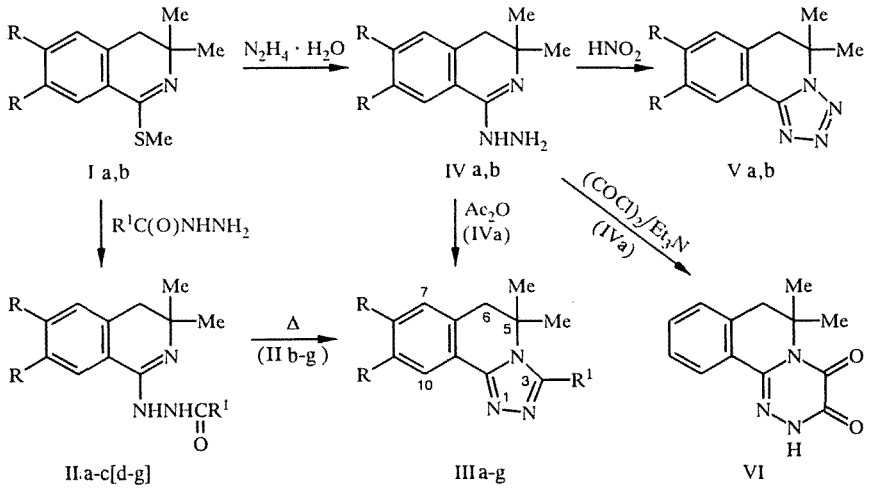
The reaction of 1-methylthio-3,3-dimethyl-6,7-di-R-dihydroisoquinolines with carboxylic acid hydrazides gives the corresponding hydrazides converted into derivatives of 1,2,4-triazolo[3,4-a]isoquinoline. Reaction of these dihydroisoquinolines with hydrazine hydrate gives the corresponding 1-hydrazinoderivatives which with $NaNO_2$ give tetrazolo[5,1-a]isoquinolines, and with oxalyl chloride (where R = H), 1,2,4-triazino[5,1-a]isoquinoline.

Condensed heterocyclic systems attract interest as potential biologically active compounds [1]. There are examples in the literature of the synthesis of such systems based on lactim ethers of the 1,3-benzoxazine system and its derivatives [2]. At the same time, there is virtually no information of the analogous conversion of the closely-related 3,4-dihydroisoquinoline derivatives. This is probably connected with the poor accessibility of the corresponding dihydroisocarbostyrils [3]. It was of interest to study the analogous reaction, described in [2], of 1-methylthio-3,3-dimethyl-6,7-di-R^1-3,4-dihydroisoquinolines (Ia, b) with branching at the $C_{(3)}$ atom which can significantly affect the course of the reaction.

It was established that during reaction with carboxylic acid hydrazides the thioethers Ia, b give the corresponding N-substituted hydrazides (IIa-c) — see scheme below. A study of the IR spectrum of these products showed that the isoquinoline fragment is found in the imine form stabilized by intramolecular hydrogen bonding. Evidence for this is provided by the absence of any shift in the absorption bands of the NH group at 3170-3190 and 3270-3300 cm^{-1} on passing from the condensed phase to a chloroform solution.



I, IV, V a R = H, b R = MeO; II, III a R = H, R^1 = Me; b R = H; R^1 = C_6H_5; c R = H, R^1 = *o*-$CH_3C_6H_4$; d R = H, R^1 = *o*-$NO_2C_6H_4$; e R = H, R^1 = 2-furyl ; e R = MeO, R^1 = C_6H_5; g R = MeO, R^1 = 2-furyl

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TABLE 1. Characteristics of Compounds II-IV

Compound	Empirical formula	mp, °C	IR spectrum, ν cm^{-1}	PMR spectrum, δ ppm*, J Hz	Yield, %
IIa	$C_{13}H_{17}N_3O$	187...188	1650, 3195 (br.)	1,24 (6H, s, $2CH_3$); 2,23 (3H, s, CH_3CO); 2,77 (2H, s, CH_2); 5,73 (1H, br. s, NH); 7,22...7,97 (4H, m, H_{arom}); 9,72 (1H, br. s, NH)	66
IIb	$C_{18}H_{19}N_3O$	220...222	1557, 1575, 1609, 1631, 1655, 3170, 3270	1,21 (6H, s, $2CH_3$); 2,83 (2H, s, CH_2); 6,70 (1H, s, NH); 6,88...8,20 (9H, m, H_{arom}); 10,19 (1H, br. s, NH)	57
IIc	$C_{19}H_{21}N_3O$	226...233	1622, 1642, 3220 (br.), 3310 (br.)	1,19 (6H, s, $2CH_3$); 2,36 (3H, s, $\underline{CH_3}C_6H_4$); 2,81 (2H, s, CH); 6,53 (1H, br. s, NH); 7,33 (7H, m, H_{arom}); 8,06 (1H, d, 8-H); 10,01 (1H, br. s, NH)	71
IIIa*[2]	$C_{13}H_{15}N_3$	154...155	1505, 1577	1,56 (6H, s, $2CH_3$); 2,62 (3H, s, CH_3); 3,03 (2H, s, CH_2); 7,28...8,13 (4H, m, H_{arom})	71
IIIb	$C_{18}H_{17}N_3$	210...211	1208, 1253, 1595, 1604	1,25 (6H, s, $2CH_3$); 2,94 (2H, s, CH_2); 7,25...7,43 (8H, m, H_{arom}); 8,13 (1H, m, 10-H)	68
IIIc	$C_{19}H_{19}N_3$	157...158	1595, 1620	1,10 (3H, s, 5-CH_3); 1,23 (3H, s, 5-CH_3); 2,13 (3H, s, $\underline{CH_3}C_6H_4$); 3,02, 3,22 (2H, 2c, CH_2, J_{AB} = = 16,4); 7,39 (7H, m, H_{arom}); 8,04 (1H, m, 10-H)	91
IIId	$C_{19}H_{16}N_4O_2$	194...194,5	1359, 1545, 1585, 1626	1,22 (3H, s, 5-CH_3); 1,30 (3H, s, 5-CH_3); 3,13 (2H, s, CH_2); 7,49 (3H, m, 7,8,9-H); 7,91 (3H, m, 4'-, 5'-, 6'-H); 8,04 (1H, m, 10-H); 8,30 (1H, dd, $J_{3',4'}$ = 8,1; $J_{3',5'}$ =1,9; 3'-H)	94
IIIe	$C_{16}H_{15}N_3O$	195...197	767, 1244, 1298, 1586, 1622	1,34 (6H, s, $2CH_3$); 2,90 (2H, s, CH_2); 6,48 (1H, dd, 4'-H); 7,12 (1H, dd, 3'-H); 7,32....7,47 (3H, m, 7,8,9-H); 7,98 (1H, d, 10-H); 8,07 (1H, dd, 5'-H)	80
IIIf	$C_{20}H_{21}N_3O_2$	248...251	758, 1010, 1055, 1109, 1208, 1253, 1604	1,25 (6H, s, $2CH_3$); 2,87 (2H, s, CH_2); 3,85 (3H, s, 8-CH_3O); 3,91 (3H, s, 9-CH_3O); 6,65 (1H, s, 7-H); 7,43 (5H, m, H_{arom}); 7,68 (1H, s, 10-H)	81
IIIg*[3]	$C_{18}H_{19}N_3O_3$	230...232	854, 890, 986, 1006, 1022, 1058, 1106, 1210, 1258, 1430, 1490, 1606	1,40 (6H, s, 5-CH_3); 2,96 (2H, s, CH_2); 3,92, 3,96 (6H, 2d, CH_3O); 6,55 (1H, dd, $J_{3',4'}$ = 4; $J_{4',5'}$ = = 2; 4'-H); 6,72 (1H, s, 7-H); 6,86 (1H, dd, $J_{3',5'}$ = 1; $J_{3',4'}$ = 4; 3'-H); 7,59 (1H, dd, $J_{3',5'}$ = 1; $J_{4',5'}$ = 2; 5'-H); 7,70 (1H, s, 10-H)	78
IVa	$C_{11}H_{15}N_3$	85...86	1586, 1620, 3200 (br.), 3316	1,23 (6H, s, $2CH_3$); 2,77 (2H, s, CH_2); 4,07 (2H, br. s, NH_2); 4,93 (1H, br. s, NH); 7,13 (3H, m, H_{arom}); 8,16 (1H, d, 8-H)	72
IVb	$C_{13}H_{21}N_3O_2$	91...92	1098, 1258, 1514, 1570, 1602, 3175, 3275...3350 (br.)	1,25 (6H, s, $2CH_3$); 2,73 (2H, s, CH_2); 3,86 (3H, s, CH_3O); 4,88 (1H, br. s NH); 6,56 (1H, s, 5-H); 7,44 (1H, s, 8-H)	66
Va	$C_{11}H_{12}N_3$	78...79	1542, 1578, 1610	1,25 (6H, s, $2CH_3$); 3,13 (2H, s, CH_2); 7,33...7,50 (3H, m, H_{arom}); 8,07 (1H, s, 8-H_{arom})	64
Vb*[4]	$C_{13}H_{18}N_4O_2$	184...186	1022, 1250, 1502, 1586, 1610	1,32 (6H, s, $2CH_3$); 3,07 (2H, s, CH_2); 3,87 (3H, s, CH_3O); 3,90 (3H, c, CH_3O); 6,76 (1H, s, 7-H); 7,55 (1H, s, 10-H)	78
VI	$C_{13}H_{13}N_3O_2$	187...188	1650, 1690	1,20 (6H, s, $2CH_3$); 2,16 (2H, s, CH_2); 6,36...7,03 (4H, m, H_{arom}); 9,58 (1H, br.s , NH)	45

*Spectra of compounds IIa, IIIb, e, g in $CDCl_3$; compounds IIb, c, d, IIIc, d in $(CD_3)_2SO$.

*[2]Mass spectrum: M^+ 273.

*[3]Mass spectrum: M^+ 325 (100), 310 (96), 294 (20), 266 (6), 155 (6), 115 (4).

*[4]Mass spectrum: M^+ 260 (100), 231 (40), 217 (73), 190 (36), 176 (62), 160 (14), 146 (13).

Attempts to cyclize the hydrazides IIa-c by the action of concentrated H_2SO_4 or $POCl_3$ were not successful but the thermal cyclization of compounds IIb, c was achieved in o-dichlorobenzene at bp leading to 3-substituted 1,2,4-triazolo[3,4-*a*]isoquinolines (IIIb, c) in good yield. It should be noted that the analogous compounds IIIe-g were obtained while attempting to prepare hydrazides IIe-g: under the conditions of the reaction (methanol at bp) the latter rapidly cyclized. Only in the IR spectrum of the unpurified products were there low-intensity bands at 3140 and 3240 cm^{-1} assigned to stretching vibrations of the NH group.

Compound IIIa was prepared from 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline (IVa) by heating the latter in acetic anhydride at bp. Compound IVa and its dimethoxy derivative (IVb) were prepared from thioethers Ia and Ib, respectively, by heating with excess hydrazine hydrate in alcohol at bp.

Treatment of a solution of hydrazines IVa, b in acetic acid with sodium nitrite in the cold leads to the corresponding 5,5-dimethyl-5,6-dihydrotetrazolo[5,1-*a*]isoquinolines (Va, b).

Reaction of hydrazine IVa with oxalyl chloride gives 7,7-dimethyl-5,6-dioxo-7,8-dihydro-1,2,4-triazino[3,4-*a*]isoquinoline (VI) in good yield while a similar reaction of this hydrazine with chloroacetyl chloride leads to extensive tar formation.

A study of a computer model of compound III using the Alchemy II program showed that the aryl substituent in position 3 cannot be positioned coplanar with the plane of the triazoloisoquinoline system because there are substituents on $C_{(5)}$ and free rotation around the $C_{(3)}$-$C_{(1')}$ bond is not possible. In fact, in the PMR spectra of compounds IIIb-f in cases where there was no o-substituent on the aryl radical, the signals for the protons on $C_{(6)}$ and the gem-dimethyl groups were observed as singlets whereas in the presence of an o-substituent the methyl group protons gave two signals. Moreover, it would seem that the geometry of the isoquinoline ring is distorted on account of repulsion between the bulky substituents, and the $C_{(6)}$ atom is out of the plane of the molecule, evidence for this being provided by a typical AB type spectrum for the protons of the CH_2 group for these compounds. The latter are formed as a racemic mixture of atropoisomers. Thus, the magnetic nonequivalence of the groups of protons at $C_{(3)}$ and $C_{(6)}$ in o-substituted triazoloisoquinolines is explained by their diastereotopicity.

EXPERIMENTAL

Infrared spectra were run on a UR-20 instrument as mulls in mineral oil. PMR spectra were recorded for 3-5% solutions in $CDCl_3$ or $(CD_3)_2SO$ on a Bruker WP-80 FY spectrometer with a working frequency of 80 MHz at 25°C. The internal standard was HMDS. Mass spectra were obtained on a Hitachi M-80 with direct injection of the sample to the ion source and an ionizing energy of 70 eV.

Monitoring of product purity was carried out by TLC on Silufol UV-254 plates in 9:1 chloroform–acetone. A 0.5% solution of chloranil in benzene was used as the detecting agent.

The characteristics of the compounds prepared are given in Table 1.

Results of elemental analysis were in agreement with those calculated.

Compound I has been described previously in [4].

1-Methylthio-6,7-dimethoxy-3,3-dimethyl-3,4-dihydroisoquinoline (Ib) was prepared by the method of [4]. mp 64-65°C (from hexane). PMR spectrum, δ ppm ($CDCl_3$): 1.04 (6H, s, $2CH_3$), 2.27 (3H, s, $S-CH_3$), 2.51 (2H, s, CH_2), 3.77 (6H, s, $2CH_3$), 6.50 (1H, s, 5-H), 7.03 (1H, s, 8-H), Yield 58%.

Substituted N'-(3,3-dimethyl-3,4-dihydroisoquinolyl-1)hydrazides (IIa-c) and 3-aryl-5,5-dimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolines (IIId-g). A mixture of 10 mmoles thioether I and 10 mmoles of the corresponding hydrazide in 25 ml methanol was heated at bp for 0.5-1 h. The reaction mixture was cooled and the precipitate which separated was recrystallized from alcohol.

3-R^1-5,5-Dimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (IIIb, c). A solution of 10 mmoles compound IIb, c in 15 ml o-dichlorobenzene was heated 2-5 h at bp. The precipitate which formed was recrystallized from alcohol.

1-Hydrazino-3,3-dimethyl-6,7-di-R-3,4-dihydroisoquinolines (IVa, b). Thioether Ia, b was heated with an excess of hydrazine hydrate in alcohol for 6 h under nitrogen, cooled, and the precipitate separated and crystallized from hexane. When equivalent quantities of thioether and hydrazine hydrate were used only up to 10% of 1,2-bis(3,3-dimethyl-3,4-dihydroisoquinolyl-1)hydrazine was formed. mp 157-159°C (from ethyl acetate). PMR spectrum, δ ppm: 1.25 (12H, s, $4CH_3$), 2.77 (4H, s, $2CH_2$), 4.97 (2H, s, 2NH), 7.18-8.10 (8H, m, H_{arom}).

3,5,5-Trimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (IIIa). Compound IVa was heated 1 h in acetic anhydride at bp. The reaction mixture was diluted with water, rendered alkaline with aqueous ammonia, extracted with chloroform, and the product crystallized from a mixture of ethyl acetate and hexane.

5,5-Dimethyl-5,6-dihydrotetrazolo-8,9-di-R-[5,1-*a*]isoquinolines (Va, b). A solution of 380 mg (2 mmoles) hydrazine IVa, b in 5 ml acetic acid was cooled to 0°C and a solution of 140 mg (2 mmoles) sodium nitrite in 5 ml water added dropwise with stirring. After 12 h the reaction mixture was diluted with water, neutralized with aqueous ammonia to pH 6, and the product filtered off and recrystallized from ethanol.

6,6-Dimethyl-3,4-dioxo-6,7-dihydro-1,2,4- triazino[6,5-*a*]isoquinoline (VI). An ether solution of a mixture of hydrazine IVa and triethylamine was added to an ether solution of oxalyl chloride in the cold. The reaction mixture was kept for 2 h at 20°C and the triethylamine hydrochloride filtered off, the filtrate evaporated, and the residue crystallized from isopropanol.

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