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PROPERTIES OF 3,3-DIALKYL-3,4-DIHYDRO-ISOQUINOLINE CYCLIC AZOMETHINES

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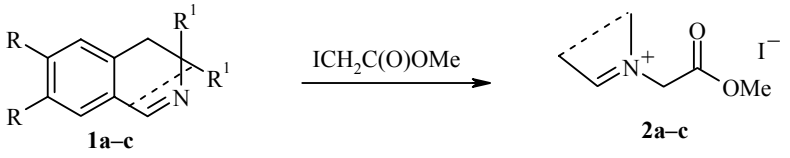
The reactions of 3,3-dialkyl-3,4-dihydroisoquinoline cyclic azomethines with the methyl ester and p-toluidide of iodoacetic acid gave stable quaternary ammonium salts which were suitable dipoles for [3+2] cycloaddition reactions. Azomethines activated by iodomethylation react with potassium cyanide and malonodinitrile.

Keywords: 3,3-dialkyl-3,4-dihydroisoquinolines, methyl ester and *p*-toluidide of iodoacetic acid, quaternary ammonium salts, dipolar [3+2] cycloaddition, reaction with potassium cyanide and malonodinitrile.

Amongst cyclic azomethines isoquinoline derivatives [1] have greatest value in organic synthesis. We have previously prepared 3,3-dialkyl-3,4-dihydroisoquinoline cyclic azomethines [2, 3]. The chemical properties of these compounds have been little studied up to this time. The aim of our work was to study their reaction with nucleophiles. The goal of the work was also to clarify the use of the named cyclic imine salts as potential dipoles in [3+2] cycloaddition reactions.

Studies have shown that compounds **1a-c** react with methyl iodoacetate to form the stable iodides **2a-c**. The base **1c** forms salt **2d** similarly with iodoacetic acid *p*-toluidide. A study of the properties of compounds **1a-c** has shown that bases of these cyclic azomethines do not react with C-nucleophiles like KCN or malonodinitrile without activation. The desired result can be achieved by activation of the imino group *via* iodomethylation. Hence reaction of the iodomethylate of imine **1c** with potassium cyanide in alcohol gives the tetrahydroisoquinoline **3** which was characterized as the hydroiodide. The reaction of this compound with malonodinitrile occurs in the presence of sodium methylate in methanol to give the dinitrile **4**. In the absence of the MeONa the reaction mixture yielded only the starting material.



1a–c **2a–c**

1,**2 a**,**b** R = H, **c** R = MeO; **1a**,**c**, **2a** R^1 = Me; **1**, **2 b** R = $(CH_2)_5$, **2c** R^1 = Me

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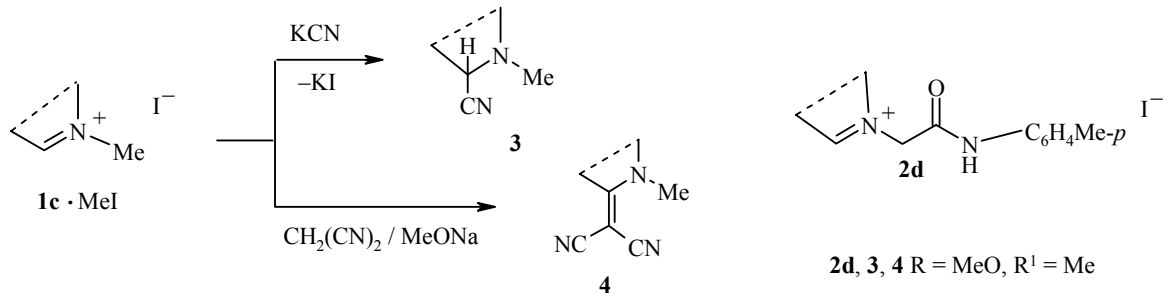
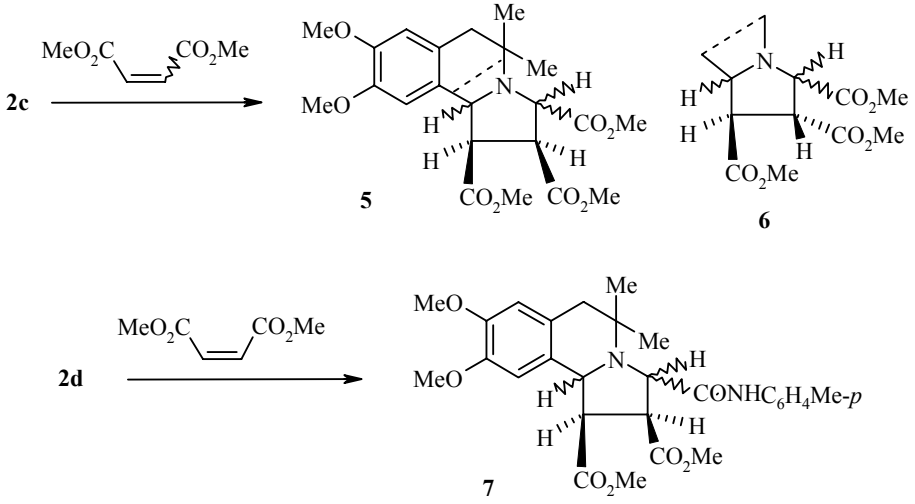


The quaternary salts **2a-d** obtained were studied as potential dipole components in cycloaddition reactions. It should be noted that most of the reactions of this type reported in the literature relate to heteroaromatic systems. The few examples of the use of 3,4-dihydroisquinolines in this reaction are given in the studies [4, 5]. A feature of compounds **2a-d** is their stability upon storage which makes them suitable as reagents. Pyridine in methylene chloride was used to generate the ylides. Reaction of the ylides obtained from salt **2c** with dimethylmaleate and dimethylfumarate gives the corresponding pyrrolo[2,1-*a*]isoquinoline derivatives **5, 6**. Similarly, the reaction of the ylide prepared from iodide **2d** with dimethylmaleate gives amide **7**. According to generally available data [4-6] dipolar cycloaddition reactions occur stereospecifically, i.e. in the case of dimethylmaleate to give the *cis*-isomer and for dimethylfumarate the *trans* isomer as a mixture of *exo* and *endo* forms [5].



All of the compounds obtained are yellow, crystalline substances. The iodides **2a-d** are sparingly soluble in water. The characteristics of for the compounds synthesized for the first time are given in Table 1.

The ^{1}H NMR spectra of the quaternary ammonium salts **2a-d** (Table 2) show a singlet H-1 proton at 9.78-10.30 ppm which is shifted to low field by about 2 ppm when compared with the shift in the starting azomethine. By contrast with the spectrum of the starting azomethine the spectrum of the compound **3** base shows an H-1 proton singlet at 4.97 ppm. The CH group signal is absent in the spectrum of base **4** which points to an enamine structure. The spectra of bases **5-7** were identified by agreement with the data in [4, 5]. The condensed tricyclic structure for the materials obtained was confirmed by the presence of four CH group doublets, two of which (2.10-2.15 ppm and 3.13-3.15 ppm) in positions 1 and 2 are complicated by the occurrence of interaction with the protons at positions 3 and 10*b*. The ^{1}H NMR spectra also show signals for the substituent, e.g. the CH_3–Ar group at 2.20 and amide group NH proton singlet at 8.73 ppm (compound **7**).

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{14}H_{18}INO_2$	46.7 / 46.8	5.0 / 5.1	40 / 39	140-141	58
2b	$C_{17}H_{22}INO_2$	51.0 / 51.1	5.5 / 5.6	3.6 / 3.5	152-154	53
2d	$C_{22}H_{27}IN_2O_3$	53.3 / 53.4	5.4 / 5.5	5.8 / 5.7	170-171	60
3	$C_{13}H_{16}IN_2 \cdot HI$	47.5 / 47.6	5.1 / 5.2	8.4 / 8.5	165-166	62
4	$C_{17}H_{19}N_3O_2$	68.6 / 68.7	6.4 / 6.4	14.2 / 14.1	138-140	71
5	$C_{22}H_{29}NO_8$	60.7 / 60.6	6.8 / 6.7	3.3 / 3.2	160-162	73
6	$C_{22}H_{29}NO_8$	60.7 / 60.6	6.8 / 6.7	3.1 / 3.2	168-170	59
7	$C_{28}H_{34}N_2O_7$	65.8 / 65.9	6.6 / 6.7	5.6 / 5.5	137-138	57

The IR spectra of esters **2a-c** contain absorption stretching bands for the ester carbonyl (1730) and the amides **2d, 7** show amide carbonyl absorption (1680) and amide N–H group bands (3250 cm^{-1}). In the nitriles **3, 4** the absorption bands for the nitrile groups are seen at 2280-2310 cm^{-1}. In the spectra of compounds **5-7** the ester group absorbs at 1735-1740 cm^{-1}. The mass spectra of esters **5, 6** were recorded for proof of their tricyclic structure and show molecular ion peaks ($[M]^+$ 435) with intensities 10 and 14% respectively. Their spectra are characterized by the presence of a peak corresponding to loss of a methoxycarbonyl group (*m/z* 376, intensities 45 and 53%).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker-300 (300 MHz) instrument using DMSO-d_6 (compounds **2b, 3, 4**) or $CDCl_3$ (compounds **2a,d, 5-7**) with HMDS as internal standard. IR spectra were taken on a Specord M-80 spectrometer using vaseline oil. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument (70 eV, EI). Confirmation of the purity of the compounds obtained was carried out using TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform (1:3:6) and revealed using UV light and iodine vapor. The synthesis of the starting azomethines, compound **2c**, and compound **1c** iodomethylate has been reported in [2, 3]. All of the compounds were recrystallized from alcohol.

N-Methoxycarbonylmethyl-6,7-(R)$_2$-3,3-(R^1)$_2$-3,4-dihydroisoquinolinium Iodides 2a-c and N-(N-*p*-tolylcarbamoylmethyl)-6,7-dimethoxy-3,3-dimethyl-3,4-dihydroisoquinolinium Iodide (2d). The methyl ester or N-*p*-tolylamide of iodoacetic acid (12 mmol) was added to a solution of the imine **1a-c** (10 mmol) in 2-propanol (5-10 ml), refluxed for 2 h, and cooled to 20ºC. The precipitate was filtered off, dried, and recrystallized.

1-Cyano-6,7-dimethoxy-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (3). A solution of KCN (0.78 g, 12 mmol) in water (5-7 ml) was added to a suspension of the imine iodomethylate **2c** (3.61 g, 10 mmol) in ethanol (30 ml). The mixture was refluxed for 1 h, solvent was evaporated *in vacuo*, and the residue was treated with aqueous ammonia. The resulting oil was extracted with ether and the ether layer was washed with water, solvent was distilled off, and HI (48%, 1.4 ml) was added to form the hydroiodide of compound **3**. The product was filtered off, dried, and recrystallized. The base compound **3** was prepared by treating the hydroiodide with a solution of ammonia.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)					
	R^1	$C\underline{H}_2CR^1{}_2$	Aromatic protons	HC=, (s)	CH_3O (s)	Other protons
2a	1.48 (6H, s, $2CH_3$)	3.25 s	7.18-8.18 (4H, m)	10.0	3.81 (3H)	5.22 (2H, s, CH_2CO)
2b	1.65 (10H, br. s, $5CH_2$)	3.15 s	7.20-8.23 (4H, m)	9.78	3.82 (3H)	5.21 (2H, s, CH_2CO)
2d	1.33 (6H, s, $2CH_3$)	3.12 s	6.47-7.46 (6H, m)	10.30	3.73 (3H); 3.75 (3H)	2.20 (3H, s, CH_3–Ar); 4.85 (2H, s, CH_2CO); 8.80 (1H, s, NH amide)
3	1.15 (6H, br. s, $2CH_3$)	2.87 s	6.38 (s, H-5); 6.88 (s, H-8)	—	3.69 (6H)	4.97 (1H, s, H-1); 2.50 (3H, s, CH_3N)
4	1.09 (6H, br. s, $2CH_3$)	3.22 s	6.40 (s, H-5); 6.87 (s, H-8)	—	3.70 (6H)	2.50 (3H, s, CH_3N)
5	1.03 (3H, s, CH_3); 1.21 (3H, s, CH_3)	2.78 (d, ^2J = 15.8)	6.41 (s, H-7); 6.53 (s, H-10)	—	3.52 (3H); 3.61 (3H); 3.64 (3H); 3.80 (3H)	4d, 4CH (4H-1,2,3,10*b*): 2.15 (^3J = 15.7); 3.15 (^3J = 8.3); 4.10 (^3J = 8.1); 4.97 (^3J = 8.2)
6	0.93 (3H, s, CH_3); 1.26 (3H, s, CH_3)	2.76 (d, ^2J = 16.0)	6.36 (s, H-7); 6.50 (s, H-10)	—	3.50 (3H); 3.60 (3H); 3.62 (3H); 3.78 (3H)	4d, 4CH (4H-1,2,3,10*b*): 2.10 (^3J = 16.0); 3.13 (^3J = 8.1); 4.20 (^3J = 8.0); 4.73 (^3J = 8.0)
7	0.94 (3H, s, CH_3); 1.23 (3H, s, CH_3)	2.80 (d, ^2J = 14.2)	6.41–7.55 (6H, m)	—	3.52 (3H); 3.61 (3H); 3.64 (3H); 3.80 (3H)	4d, 4CH (4H-1,2,3,10*b*): 2.12 (^3J = 15.7); 3.15 (^3J = 8.8); 4.23 (^3J = 7.8); 4.80 (^3J = 8.0); 2.20 (3H, s, CH_3Ar); 8.80 (1H, s, NH amide)

1-Dicyanomethylidene-6,7-dimethoxy-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (4). Sodium (1.0 gm 25 mmol) was dissolved in methanol (50 ml). Malonodinitrile (0.66 g, 10 mmol) was added to the obtained solution and the mixture was then added to a solution of the iodomethylate **2c** (3.61 g, 10 mmol) in methanol (150 ml). The mixture was refluxed for 2 h, solvent was distilled off, and the residue formed was filtered off and thoroughly washed with water, dried, and recrystallized.

Trimethyl Esters of 8,9-Dimethoxy-5,5-dimethyl-1,2,3,5,6,10b-hexahydro-1,2,3-tricarboxylic Acid (5, 6) and 1,2-dimethyl Ester of 8,9-Dimethoxy-5,5-dimethyl-1,2,3,5,6,10*b*-hexahydro-1,2,3-tricarboxylic acid 3-N-*p*-Tolylamide (7). The corresponding dipolarophile (10 mmol) was added to a solution of the appropriate quaternary ammonium salt (10 mmol) in pyridine (5-7 ml) and methylene chloride (10 ml). Heating of the solution was observed. The mixture was left for 24 h at 20ºC, methylene chloride was distilled off, and the product was diluted with water (150 ml). The precipitate was filtered off, dried, and recrystallized.

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