CHEMISTRY OF BICYCLIC UREAS.

6. SYNTHESIS OF 2,4,8,10-TETRAAZABICYCLO[4.4.0]-3,9-DECANEDIONES

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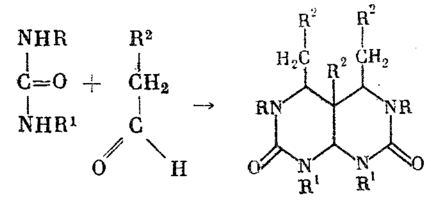
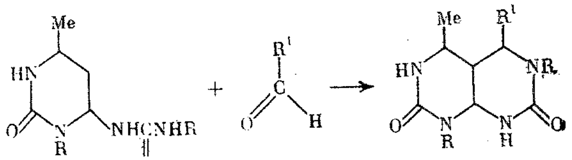
Bicyclic bisureas (BBU) of the decane series are formed by the condensation of ureas with monoaldehydes in strongly acidic medium



This reaction gives good results only when acetaldehyde and the unsubstituted, monomethyl- and dimethylureas are used [1, 2]. The higher aldehydes lead to the BBU in low yield [3]. Single examples are also known of obtaining BBU of the given series from products that could be intermediates in the condensation of urea and methylurea with acetaldehyde, and specifically 6-ureidohexahydro-2-pyrimidinones (I) [1, 4]. This method makes it possible to obtain BBU that contain various substituents on C^7. The reaction is run by keeping a solution of the starting components at ∿20°C in the presence of HCl (1:1) for a long time. An attempt to extend this reaction to aromatic aldehydes proved unsuccessful; the BBU are obtained with difficulty and in low yields.

We developed an efficient method for obtaining BBU of the decane series from 1,4-dimethyl-6-(3'-methylureido)hexahydro-2-pyrimidinone (Ia) by replacing the homogeneous acid catalyst by the ion-exchange resin KU-2 in the acid form.



(Ia,b) (IIa-n) (IIIa-n)

R = Me (Ia); $R^1 = n\text{-Pr}$ (IIa), (IIIa); $R^1 = PhCH = CH$ (IIb), (IIIb); $R^1 = Ph$ (IIc), (IIIc); $R^1 =$ furyl (IId, (IIId); $R^1 = 4\text{-}O_2NC_6H_4$ (IIe), (IIIe); $R^1 = 2\text{-}HOC_6H_4$ (IIg), (IIIg); $R^1 = 3\text{-}HOC_6H_4$ (IIh), (IIIh); $R^1 = 4\text{-}MeOC_6H_4$ (IIi), (IIIi); $R^1 = 3\text{-}O_2NC_6H_4$ (IIk), (IIIk); $R^1 = 4\text{-}BrC_6H_4$ (IIl), (IIIl); $R^1 = 4\text{-}HO\text{-}3\text{-}MeOC_6H_3$ (IIm), (IIIm); $R^1 = 3,4\text{-}(MeO)_2\ C_6H_3$ (IIn), (IIIn); when $R = i\text{-Pr}$ (Ib), $R^1 = Ph$ (IIc), (IIIc).

The developed method makes it possible to shorten the reaction time from several days to one hour and greatly expands the gamut of employed aldehydes.

In the case of the reaction of (Ia) with butyraldehyde (IIa) and of 4-methyl-1(3)-isopropyl-6-(3'-isopropylureido)hexahydro-2-pyrimidinone (Ib) with benzaldehyde (IIc) the BBU (IIIa) and (IIIf) are formed only in the presence of HCl. The results of the studies are given in Tables 1 and 2.

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TABLE 1. Preparation of 2,4,8,10-Tetraazabicyclo[4.4.0]decanediones (III) in the Presence of Concentrated HCl

BBU	Starting compounds, mmoles		Solvent, ml	Time of holding, days	Yield, %	mp, °C (solvent)	R_f	Found/calc., %			Empirical formula	Infrared spectrum ν, cm^{-1}
	(I)	(II)						C	H	N		
(IIIa)	(Ia), 12	(IIa), 37	70% alcohol, 25	5	9	292–292,5 (from *i*-PrOH) cf. [1]	0,44	–	–	22,75 22,12	$C_{12}H_{22}N_4O_2$	1660 and 1688 (C=O) 2970 (CH), 3290 (NH)
(IIIb)	(Ia), 2,5	(IIa), 13	Alcohol, 5	4	5	273–275 (from MeOH)	0,69	–	–	17,84 17,82	$C_{17}H_{22}N_4O_2$	1530 (Ph), 1656 and 1680 (C=O), 3085 (CH), 3226 and 3240 (NH)
(IIIc)	(Ia), 5	(IIc), 25	Alcohol, 5	3	55,6	306–307 (from alcohol) cf. [1]	0,67	–	–	–	–	–
(IIId)	(Ia), 10	(IId), 20	Alcohol, 15	2,5	3,4	310–312 (from DMF)	0,69 (*i*-PrOH – ether, 40 : 1)	54,87 55,00	6,63 6,63	19,86 19,72	$C_{13}H_{17}N_4O_3$	1592 (furyl) 1685 (C=O), 2985 (CH) 3225 and 3310 (NH)
(IIIe)	(Ia), 2,5	(IIe), 2,5	Alcohol, 10	4	7,2	242–243 (from DMF)	–	54,12 54,05	6,05 5,74	–	$C_{15}H_{19}N_5O_4$	1286 and 1490 (NO_2), 1585 (Ph), 1655 (C=O), 2940 (CH), 3295 (NH)
(IIIf)	(Ib), 170	(IIc), 240	70% *i*-PrOH, 500	2	50	241–242 (from aqueous *i*-PrOH)	–	66,27 66,23	8,19 8,19	–	$C_{19}H_{28}N_4O_2$	1582 (Ph), 1680 and 1710 (C=O), 2910 (CH), 3245 (NH)

TABLE 2. Preparation of 2,4,8,10-Tetraazabicyclo[4.4.0]decanediones (III) in the Presence of KU-2

BBU	Starting compounds, mmoles		Solvent, ml	Reaction time, h	Isolation method	Yield, %	mp, °C (solvent)	R_f	Found/calc., %			Empirical formula	Infrared spectrum ν, cm^{-1}
	(Ia)	(II)							C	H	N		
(IIIb)	10	(IIb), 18	DMF, 8	2	B	39	273–275 (from MeOH)	0,69	–	–	–	–	–
(IIIc)	5	(IIc), 25	*i*-PrOH, 8	0,5	A	59	306–307 (from alcohol)	0,67	–	–	–	–	–
(IIId)	200	(IId), 400	*i*-PrOH, 450	4	A	57,5	310–312 (from DMF)	0,69	–	–	–	–	–
(IIIe)	100	(IIe), 134	*i*-PrOH, 200	3	A	67,5	259–260	–	–	–	–	–	–
(IIIg)	10	(IIg), 12	DMF, 8	2	C (MeOH–Me_2CO, 3 : 7)	45	298–299 (from water)	0,83	56,84/56,75	6,56/6,88	17,50/17,25	$C_{15}H_{20}N_4O_3 \cdot 0{,}9H_2O$	1531 (Ph), 1667 (C=O), 2982 (CH), 3030 (NH), 3340 (OH)
(IIIh)	10	(IIh), 10	*i*-PrOH, 20	2	C (DMF)	23,7	254–255 (from DMF : acetone, 1 : 2)	0,75	59,22/59,20	6,87/6,62	–	$C_{15}H_{20}N_4O_3$	1540 (Ph), 1638 and 1650 (C=O), 2935 and 3110 (CH), 3200 (NH), 3420 (OH)
(IIIi)	10	(IIi), 12	Dioxane + + *i*-PrOH (20+10) DMF, 10	2	C (DMF) B	15 43	277–278 (from DMF)	0,65	–	–	17,59/17,17	$C_{16}H_{20}N_4O_3$	1520 (Ph), 1660 (C=O), 2973 and 3074 (CH), 3224 and 3306 (NH)
(IIIk)	10	(IIa), 15	*i*-PrOH, 28	1,5	A, B	37,6	272–273 (from MeOH)	0,6	51,78/51,90	5,72/5,94	20,23/20,29	$C_{15}H_{19}N_5O_4 \cdot 0{,}8H_2O$	1280 and 1490 (NO_2), 1540 (Ph,) 1668 (C=O), 2980 (CH), 3220 (NH), 3430 (OH)
(IIIl)	10	(IIl), 15	*i*-PrOH, 25	2	A	32,3	275–276,5 (from MeOH)	0,7	48,80/49,06	5,44/5,22	21,73/21,76	$C_{15}H_{19}N_4O_2 \cdot Br$	1580 (Ph), 1650 and 1690 (C=O), 2970 (CH), 3240 (N–H)
(IIIm)	400	(IIm), 480	*i*-PrOH, 600	3	B	36	279–280 (from i-PrOH)	–	57,24/57,65	6,82/6,35	16,51/16,80	$C_{16}H_{22}N_4O_4$	1592 (Ph), 1660 and 1680 (C=O), 2990 (CH), 3218 (NH), 3476 (OH)
(IIIn)	10	(IIn), 12	*i*-PrOH, 15	2,5	B	40	272–273 (from MeOH)	0,48	55,41/55,30	6,82/7,15	15,04/15,18	$C_{17}H_{24}N_4O_4 \cdot 1{,}2H_2O$	1525 (Ph), 1669 (C=O), 2980 (CH), 3230 (NH), 3318 (OH)

EXPERIMENTAL

The IR spectra were obtained on a UR-10 instrument (as KBr pellets). The chromatographing was done in a thin bound layer on Silufol UV-254 plates in a n-BuOH:MeOH:H_2O (3:1:1) mixture, with development by iodine vapors. 1,4-Dimethyl-6-(3'-methylureido)hexahydro-2-pyrimidinone (Ia) has the constants given in [1], while 4-methyl-1(3)-isopropyl-6-(3'-isopropylureido)hexahydro-2-pyrimidinone (Ib) was obtained the same way as (Ia). Yield 62%, mp 202-204° (from 70% alcohol), R_f 70.74. Found: C 56.70; H 9.59%. $C_{12}H_{24}N_4O_2$. Calculated: C 56.22; H 9.44%. Infrared spectrum (ν, cm^{-1}): 1667 (C=O), 2980 (CH), 3238, 3324 (NH).

General Procedures for Obtaining 2,4,8,10-Tetraazabicyclo[4.4.0]-3,9-decanediones. a) In the Presence of HCl (IIIa-f). To a solution of either (Ia) or (Ib) in EtOH were added a catalytic amount of HCl (1:1) and the aldehyde. The reaction mixture was left standing at ∿20° for several days. The (IIIa-f) precipitate was filtered and washed with acetone (see Table 1).

b) In the Presence of Cationite KU-2 (IIIb-e, g-n). To a solution of (Ia) in an organic solvent were added cationite KU-2 in the H^+ form (30% of the weight of the reactants) and the aldehyde (II). The reaction mixture was heated at 70-85°. The product was isolated by three procedures.

A) The obtained precipitate plus catalyst was filtered, dissolved in a hot solvent, the catalyst was separated and the precipitate of (III), obtained on cooling the filtrate, was filtered.

B) The hot reaction mixture was filtered from the catalyst, cooled, and the obtained (III) precipitate was separated.

C) The hot reaction mixture was filtered from the catalyst and the filtrate was evaporated in vacuo. The viscous residue was treated with a solvent and the obtained (III) precipitate was separated (see Table 2).

CONCLUSIONS

A method was developed for obtaining 2,4,8,10-tetraazabicyclo[4.4.0]-3,9-decanediones, which contain aromatic, alkaryl, and heteroaromatic substituents in the 7 position, by the condensation of 6-ureidohexahydro-2-pyrimidinones with the appropriate aldehydes in the presence of cationite KU-2 in the acid form.

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