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SYNTHESIS OF 1,3-DIAZACYCLANES BY THE BENZOYLATION OF BIS-SCHIFFS BASES

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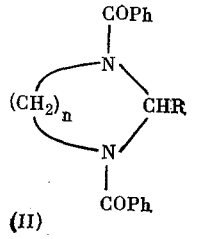
We have previously reported [1] that the acylation of bis-Schiffs bases of ethylenediamines with aromatic acid chlorides in polar media is anomalous, resulting in the formation of NN'-diaroyl-2-substituted imidazolines. We here extend this reaction to Schiffs bases with more remote azomethine groups.

As substrates for acylation we took the compounds RCH = $N(CH_2)_n$ N = CHR(I), where n and R are respectively 3, i-Pr (a); 3, Ph (b); 4, i-Pr (c); 4, Ph (d); 5, i-Pr (e); 5, Ph (f); 6, i-Pr (g); 6, Ph (h); 8, i-Pr (i); and 8, Ph (j), together with NN'-bisisobutylidene-2-methyl-1,4-diaminobutane (Ik). The acylating agent used was benzoyl chloride, the reactions with (Id, f, h, and j) being carried out in benzene and acetonitrile, and with (Ia-c, g, i, and k) in acetonitrile only. Under these conditions, the azomethines (I) (n = 3) selectively afforded the NN'-dibenzoylhexahydropyrimidines (IIa and b), but (I, $n \geqslant 4$) gave principally the noncyclic amides (III)-(V) (Table 1). Using the procedure described in [1], the Schiffs



(II)

$PhCONH(CH_2)_nNHCOPh$ (III)

$Me_2C{=}CHN(CH_2)_nNHCOPh$ (IV)
COPh

$Me_2C{=}CHN(CH_2)_nNCH{=}CMe_2$ (V)
COPh COPh

base was acylated in the presence of triethylamine, but in the case of the seven-membered heterocycles (Ic and k) it was found that the yields of cyclic products (II) were substantially increased if no triethylamine was present. For example, benzoylation of (Ic) as described in [1] afforded the diazacyclopentane (IIc) in 9% yield, whereas in the absence of triethylamine the yield was 22%. Similar variations in yield were found in the case of (IIi), and only the cyclization of (Ia and b) and the bisazomethines RCH = $N(CH_2)_2N$ = CHR was independent of the addition of triethylamine.

As will be seen from Table 1, the reaction has features similar to those of the carbon-chain compounds, since cyclization to 5- and 6-membered heterocycles was the most efficient,

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TABLE 1. Benzoylation Products of Bisazomethines

Compound	Yield, %	mp, °C	PMR, δ, ppm from HMDS ($CDCl_3$)
(IIa)	68	150–153	0,90 br.d (6H, Me), 1,2–4,8 (7H, Me_2CH and $N(CH)_{23}N$). 5,9–6,3 br (1H, NCHN), 7,34 s (10H, Ph)
(IIb)	45	178–179	1,2–5,0 (6H, $N(CH_2)_3N$), 6,8–7,9 (16H, Ph and NCHN)
(IIc)	22	166–168	0,91br.d (6H, Me), 1,7–4,5 (9H, Me_2CH and $N(CH_2)_4N$), 6,13 br.d (1H, NCHN), 7,3 s (10H, Ph)
(IId)	25	149–150	1,66 br 3,20 br, 4,13 br (8H, $N(CH_2)_4N$), 7,20 br (10H, Ph and NCHN)
(IIf)	17	238–239	1,5–4,5 (10H, $N(CH_2)_5N$), 7,0–7,5 (16H, Ph and NCHN)
(IIk)	24	106–108	0,9–2,7 (13H, Me_2CH and $MeCH(HC_2N)CH_2CH_2N$), 3,0–4,0 (4H, NCH_2), 5,87 (1H, NCHN), 7,1–8,0 (10H, Ph)
(III, n=4)	11; 65 (from (Ic); (Id))	175–177 (from [2])	
(III, n=5)	61; 81 (from (Ie); (If))	135 (from [3])	
(III, n=6)	40; 78 (from (Ig); (Ih))	163–165 (from [4])	
(III, n=8)	45; 87 (from (Ii); (Ij))	176–176,5 (from [5])	
(IV, n=4)	44 (from (Ic))	125[a]	1,15–1,85 (10H, Me and $NCH_2(CH_2)_2CH_2N$), 3,32–3,70 (4H, NCH_2), 5,74 (1H, N=CH), 7,15–7,95 (11H, Ph and NH)
(IV, n=6)	21 (from (Ig))	76–79[b]	1,2–1,5 (14H, Me and $NCH_2(CH_2)_4CH_2N$), 3,16–3,66 (4H, NCH_2), 5,67 (1H, N=CH), 6,95 br (1H, NH), 7,17–7,90 (10H, Ph)
(IV, n=8)	10 (from (Ii))	64–66[c]	1,31–2,10 (18H, Me and $NCH_2(CH_2)_6CH_2N$), 3,41–3,95 (4H, NCH_2), 5,98 (1H, N=CH), 6,68 (1H, NH), 7,38–8,00 (10H, Ph)
(V, n=6)	19 (from (Ig))	Oil[d]	1,15–2,0 (20H, Me and $NCH_2(CH_2)_4CH_2N$), 3,2–3,8 (4H, NCH_2), 5,95 (2H, N=CH), 7,2–7,7 (10H, Ph)
(V, n=8)	14 (from (Ii))	Oil[e]	1,1–2,0 (24H, Me and $NCH_2(CH_2)_6CH_2N$), 3,3–3,8 (4H, NCH_2), 5,90 (2H, N=CH), 7,1–7,6 (10H, Ph)

a-e m/z 350 (a), 378 (b), 406 (c), 432 (d), 460 (e).

the yields then falling rapidly, 1,3-diazacyclopentanes being obtained in 22-25% yields, 1,3-bisazacyclooctanes in 17-25% yields, and no higher azacyclanes were obtained at all.

These experimental findings may be rationalized by a study of Dreiding models of heterocycles containing two nitrogen atoms in the 1 and 3 positions. These systems have some common features: 1) the heterocyclic ring adopts conformations similar to those of the corresponding carbocycles in which the nitrogens are replaced by CH_2 groups; 2) in rings in which n = 5, 6, and 8 there is a transannular effect such as occurs in the corresponding carbocycles, but to a somewhat lesser extent, since the unpaired electrons on the nitrogen atoms are pulled towards the CO groups, thus decreasing the transannular overlapping of these pairs; and 3) the substituent in the 2-position (Ph or i-Pr) interacts sterically with the benzoyl groups, resulting in an increase in the conformational rigidity of the molecule as a whole, and the creation of additional steric hindrance. Effects of this type are especially great in 9- and 11-membered heterocycles. Models of compounds (IIg-j) are assembled only with difficulty, and exist in a few rigidly fixed conformations. In the case of compounds (IIa-f and k) greater conformational mobility of the ring is possible, together with rotation

(albeit restricted) of the substituents in the 1-, 2-, and 3-positions. In five- and six-membered rings, rotation of the substituents is also somewhat restricted, but the ring itself if not strained.

It follows that cyclic structures with a total number of atoms from 5 to 8 should be relatively easily obtainable, but further extension of the ring is unlikely, as found experimentally. The conclusion that the rotation of the substituents in this series of heterocycles is hindered is confirmed by their PMR spectra, in which the signals for the Me protons of the Me_2CH groups are seen as broadened, poorly resolved doublets.

The preparation of 1,3-diazacycloalkanes from bisimino-compounds is interesting and of practical value, since no such method for the preparation of such systems has been described. There has only been reported an unsuccessful attempt to obtain cyclic derivatives from NN'-diacyldiaminobutanes and aldehydes [6]. To check these results, we attempted to find conditions for the reaction of NN'-dibenzoyl-1,4-diaminobutane with benzaldehyde, but the perhydroazepine (IId) could not be detected (TLC and PMR).

EXPERIMENTAL

Melting points were determined on a Boetius block, PMR spectra were obtained on Varian DA-60 and Tesla BS-497 instruments, and mass spectra on a Varian MAT CH-6. The elemental analyses of the compounds obtained corresponded to the calculated values.

The starting bisazomethines were synthesized by reacting the appropriate α,ω-diaminoalkanes with isobutyraldehyde and benzaldehyde, as described in [1].

NN'-Di(isobutylidene)-1,3-propylenediamine (Ia), yield 30%, bp 86-88°C (13 mm) (cf. [7]).

NN'-Di(benzylidene)-1,3-propylenediamine (Ib), 85%, mp 30.5-33.5°C (from hexane) (cf. [8]).

NN'-Di(isobutylidene)-1,4-diaminobutane (Ic), yield 45%, bp 93-96°C (12 mm) (cf. [9]).

NN'-Di(benzylidene)-1,4-diaminobutane (Id), yield 91%, mp 42°C (from hexane) (cf. [10]).

NN'-Di(isobutylidene)-1,5-diaminopentane (Ie), yield 53%, bp 128-131°C (15 mm). PMR spectrum (δ, ppm, HMDS): 0.9-1.8 (18H, Me and $NCH_2(\underline{CH_2})_3CH_2N$), 2.30 m (2H, Me_2CH), 3.25 t (4H, NCH_2), 7.45 d (2H, N=CH).

NN'-Di(benzylidene)1,5-diaminopentane (If), yield 73%, mp 30°C (from hexane) (cf. [11]).

NN'-Di(isobutylidene)-1,6-diaminohexane (Ig), yield 61%, bp 137-142°C (18 mm) (cf. [12]).

NN'-Di(benzylidene)-1,6-diaminohexane (Ih), yield 88%, mp 30°C (from hexane) (cf. [13]).

NN'-Di(isobutylidene)-1,8-diaminooctane (Ii), yield 35%, bp 168-170°C (15 mm). PMR spectrum (δ, ppm, HMDS): 0.95-1.80 (24H, Me and $NCH_2(\underline{CH_2})_6CH_2N$, 2.0-2.6m (2H, $Me_2\underline{CH}$), 3.15t (4H, NCH_2), 7.45 d (2H, N=CH).

NN'-Di(benzylidene)-1,8-diaminooctane (Ij), yield 75%, mp 33-34°C (from hexane) (cf. [14]).

NN'-Di(isobutylidene)-3-methyl-1,4-diaminobutane (Ik), yield 55%, bp 135-137°C (25 mm). PMR spectrum (δ, ppm, HMDS): 0.8-3.0 (24H), 7.51 (2H, N=CH).

1,3-Dibenzoyl-2-isopropyl-1,3-diazacyclopentane (IIc). To 5.1 mmole of (Ic) and 20 ml of acetonitrile was added dropwise 10.5 mmole of benzoyl chloride. The mixture was then boiled for 30 min, evaporated, and the residue extracted with benzene to give 2.51 g of an oil which was purified by chromatography on silica gel (column height 20 cm, diam. 16 mm). Elution was with benzene, followed by a mixture of benzene and ether in proportions from 20:1.5 to 1:1, giving 0.35 g of (IIc) as a yellowish oil, R_f 0.4 (on Silufol, benzene–ether, 3:1). On trituration with ether, the oil crystallized. Also obtained was (III, n = 4), R_f 0.05, and (IV, n = 4), R_f 0.2 (on Silufol, benzene–ether, 3:1).

1,3-Dibenzoyl-2-phenyl-1,3-diazacyclopentane (IId). Obtained similarly, from 1 g (3.8 mmole) and 8 mmole of benzoyl chloride. After boiling for 30 min, the reaction mixture was

treated with 8 mmole of triethylamine, and boiling continued for a further 30 min. The reaction products were isolated as described above.

Benzoylation of the other (I) and separation of the mixtures were carried out similarly. The yields and constants of the compounds obtained are shown in Table 1.

1,3-Diazacyclooctane (IIe) was obtained chromatographically as a fraction (30% yield) containing ≥ 85% of the required compound, with R_f 0.7 (Silufol, benzene–ether, 3:1). PMR spectrum (δ, ppm from HMDS, in $CDCl_3$): 1.17 d (6H, Me), 1.57 m (7H, $NCH_2(CH_2)_3CH_2N$ and Me_2CH), 3.34 br (4H, NCH_2), 5.75 br (1H, NCHN), 7.00-7.50, 7.65-8.17 (2H, Ph).

NN'-Dibenzoyl-2-methyl-1,4-diaminobutane. Yield 52%, mp 130°C. PMR spectrum (δ, ppm from HMDS in $CDCl_3$): 0.95 d (3H, Me), 1.4-2.0 m (3H, $CH_2CH(CH_3)CH_2$), 3.1-3.7 m (4H, NCH_2), 7.1-7.9 (12 H, Ph and NH).

CONCLUSIONS

Benzoylation of the bisazomethines $R{-}CH = N(CH_2)_nN = CH{-}R$ (R = i-C_3H_7, Ph; n = 3-6.8) affords NN'-dibenzoyl-2-R-1,3-diazacycloalkanes and open-chain amides. The yields of 2-R-1,3-diazacycloalkanes are at a maximum when n = 2 and 3, decreasing rapidly as n increases.

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REACTIONS OF A HYDROXIMIC ACID CHLORIDE — A 3-IMIDAZOLINE 3-OXIDE DERIVATIVE — WITH NITROGEN-CONTAINING NUCLEOPHILIC REAGENTS AND PREPARATION OF STABLE AMIDOXIME N-OXYL RADICALS

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N-Methyl-3-imidazoline 3-oxides are "protected" nitroxyl radicals, and the reactivity of the nitrone group in these compounds therefore makes it possible to introduce a fragment that contains a nitroxyl center in "latent" form into various molecules; subsequent oxidative dealkylation leads to nitroxyl radicals [1]. The reactions of 3-imidazoline 3-oxides with electrophilic reagents with activation of the nitrone group by means of metallation [2] or protonation [3] of the latter were examined. To expand the synthetic possibilities of N-methyl-3-imidazoline 3-oxides we studied the reactions with nucleophilic reagents of a

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