STERIC FACTORS IN THE CYCLIZATION OF 4-AZAHEPTANE-2,6-DIONES TO DEHYDROPIPERID-3-ONES AND THE STEREOCHEMISTRY OF REDUCTION OF 2,2-DIMETHYL- AND 5-NEOPENTYLPIPERID-3-ONES

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In studying the regioselectivity of the cyclization of azadiketones of the type (I), it was shown that the less substituted carbonyl fulfills the function of the electrophile, and the regioisomer (II) with the smallest substituent at C^4 predominates in the cyclization products [1, 2]. For example, the ratio of the products (IIa) and (IIIa) in the acidic cyclization of the diketone (Ia) was 3.5:1 [2].

In the present communication, it is shown that this rule can be broken in certain conditions, and the sterically hindered carbonyl dominates in the formation of the new C=C bond. Thus, the regioisomer :IIb; is formed exclusively in the cyclization of the azadiketone (Ib). The cause of the high selectivity for the reaction (Ib) → (IIIb) is undoubtedly determined by the steric shielding due to the tert-butyl substituent. The structure of the product (IIIb) was shown with the aid of UV, IR, and PMR spectroscopy (cf. Experimental). Thus, the PMR spectrum contradicts the structure (IIb): There is the characteristic signal of a low-field proton (C=CHC=O) in the spectrum of the cyclization product which confirms the structure (IIIb). Moreover, the formation of only one isomer in the hydrogenation (IIIb) → (IVb) also confirms the "neopentyl structure." Besides the azadiketone (Ib), the regioselectivity of the cyclization of the diketone (Va) with geminal substitution at the carbon atom adjoining the nitrogen was also studied. It is interesting that the main reaction product (90%) is thereby the unsaturated ketone (VIa). The isomeric ketone (VIIa) is only formed in 10% yield according to the GLC data. Such regioselectivity of the cyclization reaction surpasses the selectivity for the ketone (Ia); however, it is noticeably less than the selectivity of the reaction with the N-tert-butyl ketone (Ic). In the last case, the other regioisomer (IIIc) could not generally be detected [1]. Hence, the increase in size of the substituent at the nitrogen atom of the diketones (I) shows a greater influence on the regioselectivity of the cyclization by comparison with the substitution at the methylene carbon atom. For the confirmation of the structure of the main regioisomer (VIa), the dependence of the chemical shifts (CSs) of the protons (G_i) on the concentration of paramagnetic shift reagent (PSR) was studied. It follows from the PMR spectra that both of the centers of complex formation have comparable activity due to the steric accessibility of the nitrogen function. This follows from the high values of the CS of G_i for =NH and —CH=. On increasing the concentration of the PSR, the protons of the methylene group and the protons of the geminal methyl groups have comparable rates of change of CS. This is only possible in the case for which the methyl groups occur adjacent to both of the complexing centers, i.e., at C^2 [as in (VIa)]. The inspection of models for the structure (VIIa) shows that the difference of G_i for the methylene group and the gem methyl groups should comprise an order of magnitude. Hence, the structure (VIa) for the main product of the cyclization of the diketone (Va) follows unambiguously from these data. On reduction of the ketones (IIb) and (VIa) over Pd, the corresponding 3-ketopiperidines (IVb) and (VIIIa) were obtained. Methylation of (VIIIa) gave the N-methyl analog (VIIIb). All these ketones were further studied in reduction reactions under standard conditions. The interest in the stereochemistry of the reduction of the ketones (IV) and (VIII) was determined by the circumstance that the ketone (VIII) permits the evaluation of the influence of the axial methyl at the C^2 carbon atom adjoining the carbonyl; and the ketone (IV) permits a comparison of the previously studied tert-butyl [3] and the neopentyl substituents which are distant from the carbonyl. The data on the reduction are presented in Table 1.

A characteristic feature of these reactions is the predominance of the e-alcohol for the ketones (IV) and especially for (VIII), i.e., the preferential attack at the carbonyl from the axial region. Therefore, the axial methyl at C^2 largely hinders the approach of the reagent

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TABLE 1

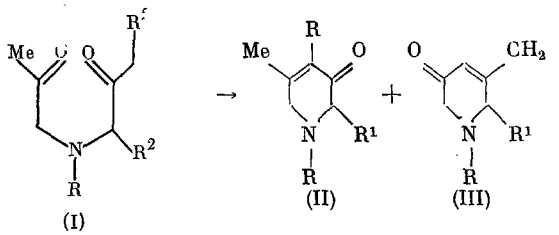
No. of batch	Conditions of reduction	Ketone (VIIIa), (VIIIb) alcohols (X) *		Ketone (IV) alcohols (IX) *	
		a, %	e, %	a, %	e, %
1	$NaBH_4 - H_2O$, 0°	0(2)	100(98)	12	88†
2	$Li - NH_3 - EtOH$ – 33°	0(5)	100(95)	15	85†
3	$PtO_2 / H_2 - H_2O$	0(2)	100(98)	31	69†
4	$Al(OPr\text{-}i)_3 - i\text{-}PrOH$‡	17(17)	83(83)	16	84†

*By GLC data, glass capillary, PÉG 40M, gas-carrier was nitrogen.
†The hydrochloride was reduced.
‡Boiling, 40 min.

along the e-coordinate, the direction of which almost coincides with the direction of the C^2-CH_3-*a* bond. The selectivity only falls insignificantly for the N-methyl analog, which confirms the closeness in the configurations of the ketones of the NH- and the NCH_3-series. By analogy, it follows from these data that the neopentyl substituent at C^5 [as in (IVb)] occupies an intermediate position between methyl and tert-butyl (cf. [3]), for the reagents Nos. 1 and 3 (cf. Table 1), for its steric influence on the axial approach of the reagent. However, this is not a strict rule, and the neopentyl surpasses even the tert-butyl for the reagents Nos. 2 and 4.

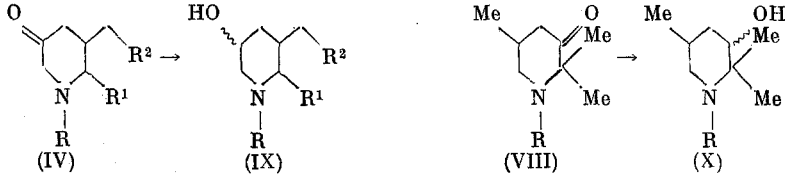
The synthesis of the initial product for the isolation of the methylneopentylketone (IV) (scheme) merits attention,

Scheme

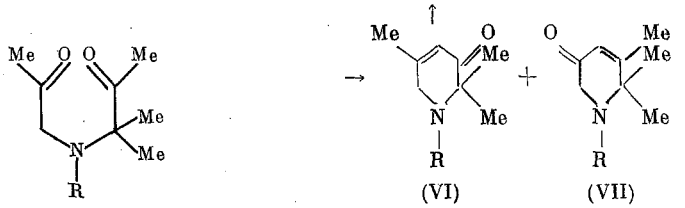


(I) (II) (III)

R = R¹ = Me, R² = H (a); R¹ = H; R = R² = *t*-Bu (b); R = *t*-Bu; R¹ = Me; R² = H (c)



(IV) (IX) (VIII) (X)



(V) (VI) (VII)

R = H (a), Me (b).

t-$BuCH_2CHX^1$—CH_2X^2 (XI)
$X^1 = X^2 = Cl$ (a)
$X^1 = Cl$; $X^2 = Br$ (b)

t-$BuCH_2CX^1$=CHX^2 (XII)
$X^1 = H$; $X^2 = Cl$ (a)
$X^1 = H$; $X^2 = Br$ (b)
$X^1 = Cl$; $X^2 = H$ (c)

t-$BuCH_2COCH_2Br$ + (*t*-BuCHBrCOMe) (XIV) (XIII)

t-$BuCH_2COCH_2NHBu$-*t* (XV)

t-$BuCH_2COCH_2N(Bu\text{-}t)CH_2C{\equiv}CH$ (XVI)

t-$BuCH_2COCH_2N(Bu\text{-}t)CH_2COMe$ (XVII)

where a favorable ratio of the regioisomers of dehydrohalogenation could be achieved with the utilization of the chlorobromide (XIb). The vinylchloride (XIII) thereby predominates (up to

70%) in the reaction products. The dichloride (XIa) mainly gives a mixture of the cis and trans isomers of (XII). Dimethylpropargylamine was utilized as a reactant for the synthesis of the ketone (VIII) (cf. scheme).

EXPERIMENTAL

1-Bromo-2-chloro-4,4-dimethylpentane (XIb). To a mixture of t-BuCl and $BrCH_2CH{=}CH_2$ (3.2 and 2.9 moles, respectively), cooled to 10°C, was added gradually 15 g of $AlCl_3$. The mixture was stirred for 30 min and diluted with water (1 liter). The organic layer was washed with $KHCO_3$, dried over K_2CO_3, and distilled. We obtained 425 g (68%) of (XIb) which was utilized without additional purification.

2-Chloro-4,4-dimethylpentene (XIIIa). a) To a mixture of 260 g of KOH, 130 ml of H_2O, and 2 g of Bu_4NBr at 76°C was added 200 g of 1,2-dichloro-4,4-dimethylpentane (XIa). The mixture was stirred at 80°C for 2 h. The product was steam distilled, dried over K_2CO_3, filtered through Al_2O_3, and distilled. We obtained 160 g of the mixture of (XIIa) and (XIIc) (65 and 35%, GLC) which we utilized directly for the isolation of methylneopentylketone (cf. below). We thereby isolated the pure (XIIa) (a mixture of 45% cis and 55% trans). PMR spectrum (CCl_4, δ, ppm): 0.90 and 0.93 singlet (9H, t-Bu), 2.0 doublet (2H, CH_2CH), and 5.8 multiplet (2H, $CH{=}CHCl$).

b) To a mixture of 400 g of KOH, 200 ml of water, and 2 g of Bu_4NBr at 80°C was added 425 g of 1-bromo-2-chloro-4,4-dimethylpentane (XIb). After treatment as in experiment a), we obtained 340 g of a mixture of (XIIa) and (XIIc) (2:1), which was utilized without separation.

4,4-Dimethylpentanone. To the mixture of 160 g of (XII) and (XIII) from experiment a) or b) was gradually added, with stirring, 50 ml of conc. H_2SO_4 with cooling to 4-5°C. The mixture was stirred for 2 h without cooling and left overnight (intense generation of HCl). The organic layer was separated [according to GLC data, this was pure (XIIa)]. The acidic layer was gradually diluted with water. The separated layer of the methylneopentylketone was washed with water, dried over K_2CO_3, and distilled. The yield of the pure ketone from the mixture of experiment b) was 100 g (96%). PMR spectrum (CCl_4, δ, ppm): 0.95 singlet (9H, t-Bu), 2.0 singlet (3H, $COCH_3$), and 2.23 singlet (2H, CH_2CO). A known sample of the ketone [4] was identical to the synthesized sample according to GLC, IR, and PMR spectra.

1-Bromo- and 3-Bromo-4,4-dimethylpentan-2-one (XIII) and (XIV). We brominated 342 g of methylneopentylketone in methanol (70 ml) at 20°C. After the addition of 48 g of bromine, the mixture was washed with water (100 and 50 ml). The mixture of the bromides was dried over K_2CO_3 and distilled on a rotary evaporator. We collected the fractions at 45-47°C (7 mm) [15 g, ketone (XIII)] and 58-60°C (7 mm) [40 g, ketone (XIV)]. The last fraction was utilized for the amination without additional purification.

1-Tert-butylamino-4,4-dimethylpentan-2-one (XV). To a solution of 35 g (0.181 mole) of the bromoketone (XIV) in 50 ml of dry acetone was gradually added 36.2 ml (0.362 mole) of t-$BuNH_2$ with cooling. After 1 h at 20°C, the mixture was filtered and the filtrate was distilled. We obtained 27 g (83%) of the aminoketone (XV) with bp 72-74°C (7-8 mm). The hydrochloride had mp 221-222°C. Found: C 59.78, H 10.81, N 6.66, and Cl 15.83%. $C_{11}H_{24}NOCl$. Calculated: C 59.59, H 10.83, N 6.33, and Cl 16.02%. IR spectrum: 1720 cm^{-1} (C=O).

1-(Tert-butylpropargyl)amino-4,4-dimethylpentan-2-one (XVI). To a mixture of 30 g of K_2CO_3, 30 ml of water, 50 ml of MeCN, and 18.5 g (0.1 mole) of the aminoketone (XV) was gradually added 12 g (0.1 mole) of propargyl bromide. The ketone (XV) disappears completely after stirring for 5 h (GLC). After the usual treatment, we obtained 21 g (94%) of the aminoketone (XVI) with bp 118°C (7-8 mm). The hydrochloride had mp 151-152°C. Found: C 64.70, H 10.07, N 5.39, and Cl 14.77%. $C_{14}H_{26}NOCl$. Calculated: C 64.74, H 10.02, N 5.39, and Cl 13.68%.

2,2-Dimethyl-6-tert-butyl-6-azanonane-4,8-dione (XVII). To 2 g of $HgSO_4$ in 50 ml of water and 18 ml of conc. H_2SO_4 was gradually added 20 g of the acetylenic ketone (XVII) with stirring. The hydration ended after 40 min (GLC). The mixture was diluted with 100 ml of water and 10 ml of ether. The mixture was neutralized with dry K_2CO_3 and cooling. The ether layer was separated, dried with K_2CO_3, filtered through Al_2O_3, and concentrated to dryness. According to the GLC data, the residue is the diketone (XVII), hydrochloride, mp 149°C. Found: C 59.93, H 10.23, N 5.17, and Cl 12.91%. $C_{14}K_{20}NO_2Cl$. Calculated: C 66.54; H 10.09, N 5.04; N 5.04; and Cl 12.79%. The ketone (XVII) was taken for further cyclization without additional purification.

1-Tert-butyl-5-neopentyl-4,5-dehydropiperid-3-one Hydrochloride (IIIb). We dissolved 18 g (0.074 mole) of the azadiketone (XVII), from the preceding experiment, in 50 ml of benzene. We added 10 ml of water, ~0.7 g of NBu_4Br, and 10 g of KOH gradually under argon. The stirring was continued for a further 30 min (control by GLC). After the usual treatment, we obtained 14 g (73%) of the hydrochloride (IIIb), mp 160-161°C. Found: C 64.75, H 9.97, N 5.34, and Cl 13.65%. $C_{14}H_{26}NOCl$. Calculated: C 64.74, H 10.02, N 5.39, and Cl 13.68%. IR spectrum (ν, cm^{-1}): 1685 (C=CC=O) and 1640 (C=C). UV spectrum (λ_{max}, nm): 235; ε 19600. PMR spectrum (CCl_4, δ, ppm): 0.96 singlet (9H, t-Bu), 1.1 singlet (9H, $NC(CH_3)_3$). 1.75 broad singlet (2H, $CH_2C(CH_3)_3$), 3.16 multiplet (2H, NCH_2CO), and 3.25 multiplet (1H, CH_2N), (1H, CHCO).

1-Tert-butyl-5-neopentylpiperid-3-one Hydrochloride (IVb). The hydrochloride (IIIb) was hydrogenated in water over Pd/C. After crystallization from acetone, we obtained (IVb), mp 184-185°C. Found: C 64.19, H 10.64, N 5.32, and Cl 13.62%. $C_{14}H_{28}NOCl$. Calculated: C 64.29, H 10.70, N 5.35, and Cl 13.57%. IR spectrum (ν, cm^{-1}): 1720 (C=O).

The Hydrochloride of the e-Epimer of 1-Tert-butyl-5-neopentylpiperid-3e-ol (IX). The mixture of the isomeric alcohols from the $NaBH_4$ reduction (cf. Table 1) was crystallized in the form of the hydrochlorides from MeOH–EtOAc. We obtained the pure e-(IX) [the yield was 1.7 g from 2 g of (IVb)], mp 212°C. Found: C 63.70, H 11.45, N 5.34, and Cl 13.45%. $C_{14}H_{30}NOCl$. Calculated: C 63.76, H 11.39, N 5.31, and Cl 13.47%. IR spectrum (0.005 M in CCl_4): 3600 cm^{-1} (free OH).

The Hydrochloride of the α-Epimer of 1-Tert-butyl-5-neopentylpiperid-3-ol (IXa). The mixture of the alcohols from the hydrogenation of 2 g of (IVb) was subjected to fractional crystallization from MeOH–EtOAc. We obtained 0.4 g of the pure α-(IX), mp 159°C. Found: C 63.7, H 11.45, N 5.34, and Cl 13.36%. $C_{14}H_{30}NOCl$. Calculated: C 63.76, H 11.39, N 5.31, and Cl 13.47%. IR spectrum (0.005 M in CCl_4): 3490 cm^{-1} (bound OH).

N-Acetonyl-N-dimethylpropargylamine. To the mixture of 35 g (0.42 mole) of dimethylpropargylamine, 70 g of K_2CO_3, 50 ml of water, and 100 ml of benzene was added 58 g (0.42 mole) of bromoacetone with moderate cooling (30°C). At the conclusion of the reaction (GLC), the product was crystallized from cooled pentane. We obtained 49 g (87.4%) of the pure amine with mp 34-35°C. Found: C 69.05, H 10.41, and N 9.06%. $C_8H_{13}NO$. Calculated: C 69.00, H 10.07, and N 9.85%.

4-Aza-3,3-dimethylheptane-2,6-dione (Va). We treated 3 g of the amine from the preceding experiment with 3.5 ml of conc. H_2SO_4, 10 ml of water, and 0.15 g of $HgSO_4$. After filtering through Al_2O_3, the ethereal extract of the reaction product was acidified with aqueous HCl. After the usual treatment and crystallization from n-BuOH–EtOAc, we obtained 3.4 g (85%) of the hydrochloride (Va), mp 188-189°C. Found: C 50.08, H 8.44, N 7.50, and Cl 18.37%. $C_8H_{16}NOCl$. Calculated: C 49.61, H 8.27, N 7.23, and Cl 18.37%.

The Hydrochloride of 2,2,5-Trimethyl-4,5-dehydropiperid-3-one (VIa)•HCl. We obtained the hydration product (Va) (control by GLC) from 3.9 g (0.1 mole) of N-acetonyl-N-dimethylpropargylamine in the conditions of the preceding experiment (40 ml of water, 14 ml of conc. H_2SO_4, and 3 g of $HgSO_4$). The mixture was heated, without separation, for 2 h in vacuo at 70°C. After the usual treatment, we obtained 10 g (63%) of the hydrochloride (VIa), mp 209-210°C. Found: C 54.68, H 8.04, N 8.0, and Cl 19.73%. $C_8H_{14}NOCl$. Calculated: C 54.70, H 7.98, and Cl 20.22%. IR spectrum (ν, cm^{-1})L 1690 (C=CC=O) and 1645 (C=O). UV spectrum: λ_{max} 229 nm, ε 17500. PMR spectrum (CCl_4, δ, ppm): 1.28 singlet (6H, $C^2(CH_3)_2$, −2.31), 1.91 multiplet (3H, C^5–CH_3, G_i 1.00), 1.95 broad singlet (1H, NH, G_i 26.20), 3.51 multiplet (2H, CH_2H, G_i 2.42), and 5.83 q (1H, =CH–CO, J = 1.4 Hz).

The Hydrochloride of 2,2,5-Trimethylpiperid-3-one (VIIIa)•HCl. We hydrogenated 5.6 g of the hydrochloride (VIa) in 20 ml of water over Pd/C. After crystallization from n-BuOH (traces)–acetone, we obtained 5.4 g (96%) of the hydrochloride (VIII), mp 200.5°C. Found: C 54.21, H 9.20, N 7.97, and Cl 19.65%. $C_8H_{16}NOCl$. Calculated: C 54.08, H 9.01, N 7.89, and Cl 20.00%. IR spectrum (ν, cm^{-1}): 1720 (C=O).

The Hydrochloride of 1,2,2,5-tetramethylpiperid-3-one (VIIIb)•HCl. The base (VIIIa) was methylated with MeI–K_2CO_3 in aqueous acetone. We obtained 2.1 g (84%) of the hydrochloride (VIIIb) from 2.4 g of (VIIIa)•HCl. The hydrochloride (VIIIb) had mp 196-196.5°C (from acetone–MeOH). Found: C 56.90, H 9.36, N 7.34, and Cl 18.55%. $C_9H_{18}NOCl$. Calculated: C 56.60, H 9.39, N 7.31, and Cl 18.53%. IR spectrum (ν, cm^{-1}): 1720 (C=O).

The Hydrochloride of the e-Isomer of 2,2,5-Trimethylpiperid-3-ol e-(Xa). The solution of 2 g of (VIIIa)•HCl in 10 ml of water was hydrogenated over Pt (from PtO_2). After crystallization from MeOH–EtOAc, we obtained 1.98 g of e-(Xa)•HCl, mp 236°C. Found: C 53.43, H 10.00, N 7.51, and Cl 19.72%. $C_8H_{10}NOCl$. Calculated: C 53.48, H 10.03, N 7.80, and Cl 19.77%. IR spectrum (0.005 M, CCl_4, ν, cm^{-1}): 3600 (free OH).

The Hydrochloride of the e-Isomer of 1,2,2,5-Tetramethylpiperid-3-ol e-(Xb). This was obtained from (VIIIb) and had mp 204°C (from acetone). Found: C 55.75, H 10.20, N 7.34, and Cl 18.34%. $C_9H_{20}NOCl$. Calculated: C 55.81, H 10.33, N 7.23, and Cl 18.34%.

The α-Epimers of 2,2,5-Trimethyl- and 1,2,2,5-Tetramethylpiperid-3-ols α-(Xa) and α-(Xb). The α-epimers of these alcohols were not isolated in pure form. The content in the mixture was determined with the aid of GLC (glass capillaries, PEG 40M). The α-epimers emerge before the e-epimers. The N-methyl analog was identified by the methylation (MeI–H_2CO_3) of the mixture of the e- and α-epimers of the NH analogs.

CONCLUSIONS

1. The neopentyl substituent in the azadiketones of the type (Ib) completely blocks the cyclization to the dehydropiperidine systems with the participation of the acetonyl carbonyl as the electrophile.

2. In such azadiketones, the geminal substitution at the carbon atom adjoining the nitrogen is less effective in its influence on the regioselectivity of the cyclization by comparison with the influence of substitution at the nitrogen.

3. In the saturated 3-ketopiperidines, the axial substituent at C^2 largely blocks the e-coordinate of the approach of the hydride nucleophiles to the carbonyl or the e-adsorption in catalytic hydrogenation. The steric influence of the neopentyl substituent at C^2 on the carbonyl depends on the specificity of the particular reagent and can surpass the influence of the tert-butyl group.

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