3-Methyl-4-oxo-5-(2-quinolyl)pentanoic Acid (IXd, $C_{15}H_{15}NO_3$) was obtained similarly in 40% yield from lactone VIId by refluxing for 15 min. Yellow crystals, mp 150-151°C (from alcohol) and $R_f 0.58$ (A). IR spectrum (KBr): 1420, 1900, 2500 (COOH), 1720 cm⁻¹ (C=O). Mass spectrum, m/z (I_{rel}, %): M⁺ 257 (26), 239 (8), 212 (10), 170 (95), 143 (100), 129 (18), 115 (46), 87 (15), 43 (15).

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SYNTHESIS OF 1-SUBSTITUTED-3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINES

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The Ritter reaction between β -substituted propionitriles and dimethylbenzylcarbinols gives 3,3-dimethyl-3,4dihydroisoquinolines containing substituents in the 1-position corresponding to those in the starting nitrile.

The Ritter reaction has been successfully used for synthesizing 3,4-dihydroisoquinolines and other heterocyclic systems [1]. Certain rules are known which govern the course of the cyclization [2]. Comparatively little work has been reported on the preparation of 3,4-dihydroisoquinolines containing 1-substituted alkyl derivatives, however. These derivatives can be valuable in preparing condensed polycyclics having the isoquinoline fragment and also alkaloids of the isoquinoline series.

We have synthesized novel compounds of this type using the Ritter reaction between the carbinols I or II and β -substituted propionitriles III

 $\begin{array}{c} E \\ \hline \\ & \\ R^{1} \\ I, II \\ II \\$

I, IV: $R^{I} = H$; II, V: $R^{I} = OCH_{3}$; III-V: R) $a = piperidino, b = morpholino, c = NHC_{6}H_{5}$; $d = N(C_{2}H_{5})_{2}$, $e = cyclohexylamino, f = O(CH_{2})_{2}N(C_{2}H_{5})_{2}$, $g = OCH_{3}$, $h = SC_{4}H_{9}$, $i = SC_{3}H_{7}$ -iso, $j = OCH_{2}CF_{2}CHF_{2}$, k = 2-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)ethylthio, $l = NHC_{6}H_{4}Br$ -p; III: $m = SCH_{2}CH_{2}CN$.

The synthesized compounds IVa-j/ and Vd,f,g were characterized as their salts VIa-j/ and VId,f,g, respectively (Table 1). The PMR spectral data for the bases are given in Table 2.

The reaction yields depend on the nature of the atom bonded to the β -carbon of the 1-alkyl substituent. Thus IVa-e and Vd having nitrogen in the side chain were obtained in yields of 93-68%, IVf,g and Vf,g with an oxygen atom 79-60%, and IVh,i with sulfur 50-22%. This is probably due to the protonation of the nitrogen and oxygen atoms under Ritter conditions (concentrated H₂SO₄) which increases the electrophilic character of the carbimmonium ions formed, thus facilitating the closing of the heterocycle.

The structures of IVa-*l* and Vd, f, g were confirmed by IR and PMR spectroscopy which show them to be 3,4dihydroisoquinolines with an azo-methine double bond. All of the compounds show IR absorption bands at 1650-1640 cm^{-1} and the absence of a band at 3500-3100 which would characterize an NH enamine form [3].

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Compound	Empirical formula	mp, °C	Yield, %
Vla Vlb Vlc Vld Vle Vlf Vlg Vlh Vli Vli Vli Vli Vlla	$\begin{array}{c} C_{18}H_{25}N_2\cdot 2HCl\\ C_{17}H_{24}N_2O\cdot 2HCl\\ C_{17}H_{24}N_2O\cdot 2HCl\\ C_{19}H_{22}N_2\cdot 2HCl\\ C_{19}H_{28}N_2\cdot 2HCl\\ C_{19}H_{28}N_2 \cdot 2HCl\\ C_{19}H_{28}N_2O\cdot 2HClO_4\\ C_{14}H_{19}NO\cdot C_6H_3N_3O_7\\ C_{17}H_{25}NS\cdot C_6H_3N_3O_7\\ C_{16}H_{23}NS\cdot H1\\ C_{16}H_{19}F_4NO\cdot HClO_4\\ C_{26}H_{32}N_2S\cdot 2HCl\\ C_{19}H_{21}BrN_2\\ C_{19}H_{30}N_2O_2\cdot 2HCl\\ C_{21}H_{34}N_2O_3\cdot 2HCl\\ C_{21}H_{34}N_2O_3\cdot 2HCl\\ C_{19}H_{21}NC_{10}+HCl\\ C_{10}H_{20}N_{20}\cdot 2HCl\\ C_{10}$	$\begin{array}{c} 168 \dots 169 \\ .154 \dots 155 \\ 153 \dots 154 \\ 113 \dots 115 \\ 187 \dots 188 \\ 168 \dots 169 \\ 139 \dots 140 \\ 130 \dots 132 \\ 191 \dots 192 \\ 182 \dots 184 \\ 197 \dots 199 \\ 70 \dots 70,5 \\ 59 \dots 61 \\ 182 \dots 183 \\ 147 \dots 148 \end{array}$	$23 \\ 68 \\ 69 \\ 72 \\ 91 \\ 79 \\ 65 \\ 22 \\ 37 \\ 48 \\ 50 \\ 62 \\ 75 \\ 68 \\ 60 \\ $

TABLE 1. Parameters for the Salts VIa-1, VIId, f, g, and the Base IVm

TABLE 2. PMR Spectral Data for IVa-l and Vd,f,g

	Chemical proton shift, ppm*				
Com- pound	4-H (2H, S)	α -CH ₂ (2H,t)	β - CH ₂ and R**	aromatic protons	
IVa	2,67	2,30	1,36 (6H, m, 3-II, 4-H); 2,402,53 (6H, m, β -CH ₂ , 2,H)	6,837,50	
IVb	2,60	2,32	2.402,53 (6H, m, β -CH ₂ , 2-H); 3,44 (4H, t, 3-H)	6,70	
IVc	2,50	2,77	3,30 (2H, t, β-CH ₂); 4,40 (1H, s, 2-H)	6,337,50	
IVd	2,80	2,20	0,90 (6H, t, 3-H); 2,302,60 (6H, m, β-CH ₂ , 2-H)	(2Fi, m) 6,83 7,50	
IVe	2,74	2,20	1,431,97 (10H, m, 3-H, 4-H, 5-II); 2,60 (1H, t,	(4H, m) 6,777,35	
IVf	2,58	2,87	2-H); 3,00 (1H, s, 1-H) 0,87 (6H, t, 6-H); 2,202,50 (6H, m, 3-H, 5-H);	(4H, m) 6,751,50	
IVg	2,60	2,87	3.30 (2H, t, 2-H) 3.60 (2H, t, β -CH ₂); 3.37 (3H, s, 2-H)	(4 H , m) 6,837,50	
IVh			0,771,50 (3H, m. 5-H); 2,102,73 (12H, m,	(4H,m) 6,837,33	
IVi	2,50	2,80	α - CH ₂ , B - CH ₂ , 2 - H, 3 - H, 4 - H) 1,10 (6H, s, 3 - H); 3,80 (1H, s, 2 - H)	(4H, m) 6,837,43	
IVj	2,50	2,83	$3,303,70$ (4H, m, β -CH ₂ , 2-H); 5,88 (1H, t, 3-H)	(4H, m) 6,737,50	
IVk	2,50	2,67	2,97 (2H, t, β -CH ₂)	(4H, m) 6,807,50	
IVL	2,50	2,83	3,30 (2H, t, β-CH ₂); 4,36 (1H, s, 1-H)	(8H, m) 6,207,33	
Vđ	2,70	2,27	0.85 (6H, t, 3-H); 2,402,60 (6H, m, β-CH ₂ , 2-H);	(8H, s) 6,42 (1H, s)	
Vf	2,54	2,70	3,77 (6H, c, CH ₃ O) 0,85 (6H, t, 6-H); 2,302,43 (6H, m, 3-H, 5-H);	6,87 (1H, s) 6,37 (1H, s)	
Vg	2,50	2,83	3,37 (2H, t, 2-H); 3.72 (6H, s, CH ₃ O) 3,30 (3H, s, 2-H); 3,60 (2H, m, β -CH ₂); 3,80 (6H, s, CH ₃ O)	6,86 (1H, s) 6,50 (1H, s) 6,96 (1H, s)	

*For most compounds the proton signal for 3-CH₃ (6H, s) were at 1.10 ppm; for IVa 1.05, IVb 1.07, and IVf 1.08 ppm.

**The R groups (CH, CH₂, CH₃) and heteroatoms (N, O, S) are numbered starting at the heteroatom bonded to the β -CH₂ group.

The PMR spectra of IVa-*l* and Vd,f,g resemble one another in the chemical shifts of the heterocyclic protons and the two methylene groups at $C_{(1)}$ and differences are seen only for the R radical. The multiplicity, proton chemical shifts, integrated intensities, and the absence of a signal for an NH proton also show that IVa-*l* and Vd,f,g exist in the azomethine form.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer for 0.01 molar solutions in chloroform. PMR spectra were recorded on an RYa-2310 instrument with internal standard HMDS. Compound purity was monitored using TLC on Silufol UV-254 plates in chloroform—alcohol—acetone (6:3:1) with visualization by chloranil solution. The synthesis of starting carbinols and nitriles was by known methods [4-9].

Elemental analytical data for C, H, and N and halogen in IVa-l, Vd,f,g agreed with that calculated.

1-(β -R-Ethyl)-3,3-dimethyl-3,4-dihydroisoquinolines (IVa-*l*) and Their Salts (VIa-*l*) (General Method). To the corresponding β -R-propionitrile (III, 0.01 mole) in benzene (50 ml) there was added with stirring and at a temperature not exceeding 5°C concentrated H₂SO₄ (4 ml) followed by 2-methyl-1-phenylpropan-2-ol (1.5 g, 0.01 mole) in benzene (50 ml). The reaction mixture was heated for 2 h at 80°C, cooled, the aqueous layer separated, washed with benzene (2 × 25 ml), and treated with ammonia solution until alkaline. The base product was extracted with ether. After drying (anhydrous MgSO₄), the extract was treated with gaseous HCl and the crystalline hydrochloride filtered off and recrystallized from a suitable solvent. After distillation of the ether, picrates and hydriodides were prepared by treating an alcohol solution of the base with the corresponding amount of the appropriate acid. Perchlorates were prepared using 57% perchloric acid.

 $1-(\beta-R-Ethyl)$ -3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolines (Vd,f,g) and Their Salts (VIId,f,g). A mixture of concentrated H₂SO₄ (4 ml) and glacial acetic acid (2 ml) was added to the nitrile (0.01 mole) in benzene (50 ml). After addition of 2-methyl-(3,4-dimethoxyphenyl)propan-2-ol (2.1 g, 0.01 mole) the mixture was heated for 1 h at 60°C and then worked up as described above.

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