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FORMATION OF A DERIVATIVE OF 3,3,5-TRICARBONYL-1,2,3,4-TETRAHYDROPYRIDINE UNDER THE CONDITIONS OF THE HANTZSCH SYNTHESIS

B. S. Chekavichus, A. E. Sausin',
R. M. Zolotoyabko, E. E. Liepin'sh,
I. B. Mazheika, and G. Ya. Dubur

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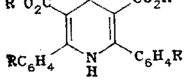
An ester of p-nitrobenzoylacetic acid is cyclized under the action of hexamethylenetetramine and ammonium acetate to 3,5-diethoxycarbonyl-3-p-nitrobenzoyl-6-p-nitrophenyl-1,2,3,4-tetra-hydropyridine, the structure of which has been established by NMR, UV, IR, and mass spectra and also by its chemical reactions.

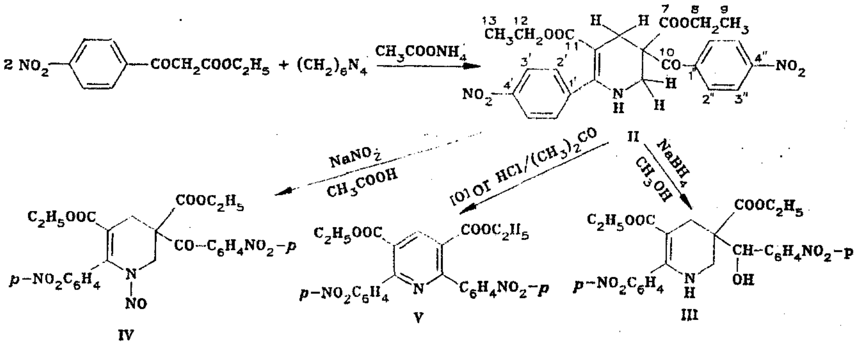
Esters of β-ketocarboxylic acids form, in different variants of the Hantzsch synthesis, 1,4-dihydropyridines. Esters of benzoylacetic acid are not excluded in this respect, although in general the reactions take place with some difficulty [1]. From an ester of p-nitrobenzoylacetic acid, 4-substituted 1,4-dihydropyridines (I, R = p-NO_2, $R^2 \neq H$) are obtained.



I

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 501-505, April, 1986. Original article submitted February 12, 1985; revision submitted June 17, 1985.

Esters of benzoyl and p-chlorobenzoylacetic acid form 4-unsubstituted 1,4-dihydropyridines (I, R^2 = H) in reaction with hexamethylenetetramine (a source of formaldehyde and ammonia) and ammonium acetate [1, 2]. However, from an ester of p-nitrobenzoylacetic acid under analogous conditions compound II is unexpectedly obtained; this does not have the 1,4-dihydropyridine structure. The long-wave maximum which is characteristic of the dihydropyridine system is absent from the UV spectrum of this compound, but there is a maximum at 272 nm. High resolution mass spectra gave for compound II an elemental composition for the group of atoms CH_2O greater than for the expected dihydropyridine. The IR spectrum gave evidence of the presence of a complex ether group at a saturated carbon atom (band at 1735 cm^{-1}). A broad band at 1690 cm^{-1} could be due simultaneously to a ketone and a complex ether group at a C=C double bond.



In order to establish the structure of compound II, ^1H and ^{13}C NMR spectra were run, the latter under conditions of full spin decoupling and without suppression of spin-spin coupling (SSC) with the protons. The appearance of three different carbonyl groups in the ^{13}C spectrum of compound II is characteristic, the resonance of $C_{(10)}$ being easily identified according to the characteristic chemical shift (195.0 ppm) and the SSC constant with the protons in positions 2 and 4 (≈1.7 Hz).

A choice between the two remaining carbonyl carbon signals was made on the basis of their SSC with the protons in positions 2 and 4. For carbon atom $C_{(7)}$ there is SSC with both groups of protons (1.4 and 1.2 Hz) while $C_{(11)}$ couples only with the protons at $C_{(4)}$ (~0.8 Hz).

Assignment of signals of atoms $C_{(2)}$ and $C_{(4)}$ does not give rise to doubt, on account of their having direct SSC constants equal to 145.2 Hz (for $C_{(2)}$) and 134.5 Hz (for $C_{(4)}$). Furthermore, atom $C_{(2)}$ additionally couples with the protons in position 4 (2.5 Hz) and also with the proton of the NH group (3.4 Hz). For the signal corresponding to carbon $C_{(4)}$ only the SSC constant with the protons in position 2 (3.7 Hz) is observed, and for $C_{(3)}$ SSC with the methylene protons in positions 2 and 4 is characteristic (3.1 Hz). The signal of atom $C_{(5)}$ is split on account of interaction with the protons in position 4.

Assignment of the signals of the aromatic carbons and those of the ethyl groups was made taking account of the data of [3].

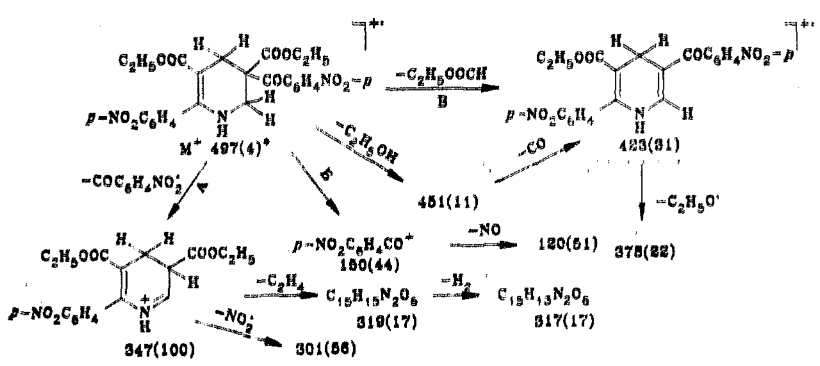
In the ^{13}C spectra of compound II, without suppression of SSC with protons, long-range SSC constants are found between amine protons and all the nearby carbon atoms ($^2J_{HNC_{(2)}}$ = 3.4, $^2J_{HNC_{(6)}}$ = 2.3, $^3J_{HNC_{(2)}C_{(3)}}$ = 3.4, $^3J_{HNC_{(6)}C_{(5)}}$ = 5.7, $^3J_{HNC_{(6)}C_{(1')}}$ = 2.3 Hz), which unequivocally support the proposed structure.

In connection with the presence of a tetrahydropyridine ring, a low intensity peak of a molecular ion (M^+, 4% of maximum) is observed in the mass spectrum of compound II, the elemental composition of which was determined at high resolution and corresponded to $C_{24}H_{23}N_3O_9$. Decay of the molecular ion takes along certain principal routes (scheme 1): 1) formation of intense even-electron ions $[M - COC_6H_4NO_2]^+$ and $NO_2C_6H_4CO^+$ as a result of rupture of the $C_{(3)}$—$C_{(10)}$ bond (routes A, B); 2) formation of an odd-electron ion $[M - HOCOC_2H_5]^+$, probably arising from conversion of the tetrahydro- to the dihydro-form (route C).

The combination of spectral data demonstrates that compound II has the structure 3,5-diethoxycarbonyl-3-p-nitrobenzoyl-6-p-nitrophenyl-1,2,3,4-tetrahydropyridine.

In the formation of the tetrahydropyridine II, in distinction from the Hantzsch synthesis of 1,4-dihydropyridines, cyclization takes place not at the expense of a carbonyl group of one

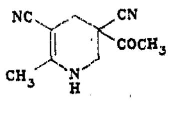
Scheme 1



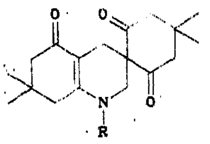
Note. Here and below: value of m/e (intensity, %).

or another molecule of the p-nitrobenzoyl ester but by way of introducing a second molecule of formaldehyde into the reaction which forms a bond with nitrogen and with the carbon of the active methylene group of the β-ketoester. Only isolated cases are observed where, in conditions of the Hantzsch synthesis, the reaction proceeds in such a direction, and 1,2,3,4-tetrahydropyridines with geminal substituents in position 3 are obtained.

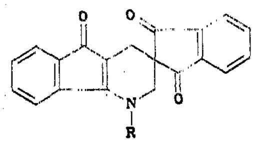
Thus, on heating β-aminocrotononitrile with hexamethylenetetramine in acetic acid with hydrochloric acid added, one obtains the tetrahydropyridine VI [4].



VI



VII



VIII

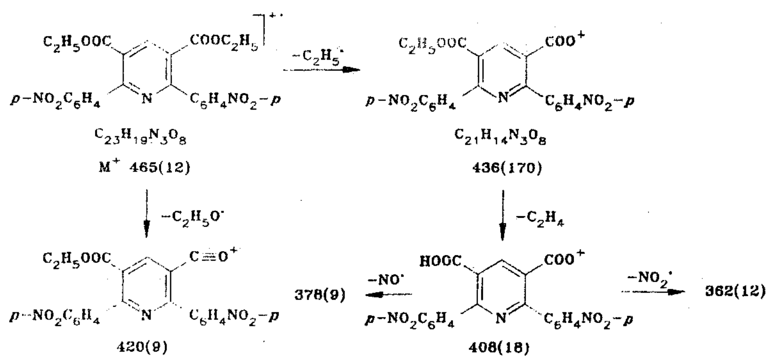
Reaction of 3-amino(3-methylamino)-5,5-dimethylcyclohex-1-ene-2-one with formaldehyde in dilute hydrochloric acid led to the spirocompound VII [5]. The similar spirocompound VIII was formed by the reaction of 1,3-indandione with amines [6].

Sodium borohydride reduces the keto group in II to an alcohol without affecting the remaining part of the molecule. In the IR spectrum of the reduced compound III a band appears characteristic of hydroxyl (3460 cm^{-1} in Nujol, shifted to 3610 cm^{-1} in chloroform solution) and two doublets are observed in the proton NMR spectrum at $\delta = 6.14$ ppm (OH) and 4.99 ppm (CH) with coupling constant $J = 4.6$ Hz.

It was not possible to prepare derivatives of the tetrahydropyridine II with reagents on the carbonyl groups and this may possibly be connected with the spatially hindered position of the geminal substituents. The action of oxidizing agents on the tetrahydropyridine II led to unexpected results. Brief (5 min) heating of II with sodium nitrite in acetic acid led to the formation of an N-nitrosoderivative. Bands for the stretching vibrations of the NH group were absent from the IR spectrum of the N-nitroso compound IV but three carbonyl bands were clearly defined at 1734, 1720, and 1700 cm^{-1}. The proton and carbon-13 NMR spectra showed little change compared with those of compound II: the signal for the protons of the 2-CH_2 group in the proton spectrum was shifted downfield and in the carbon-13 spectrum there was a large shift of $C_{(5)}$. More prolonged action of sodium nitrite in acetic acid on compound II gave a mixture of the nitroso derivative IV and 2,6-di(p-nitrophenyl)-3,5-diethoxycarbonylpyridine (V), isolated as an individual compound by the action of other oxidizing agents (selenium dioxide in acetonitrile or chloranil in benzene) on the tetrahydropyridine II. The pyridine V was also formed during an attempt at the acid hydrolysis of the ester groups of II with hydrochloric acid in acetone at elevated temperature.

In the mass spectrum of the pyridine V a more intense peak, M^+ (12% of maximum), than in the spectrum of II is observed which probably arises from the aromatic pyridine system. The main primary breakdown processes of M^+ are the formation of even-electron ions as a result of separation of the radicals C_2H_5O and C_2H_5 (scheme 2), analogous to those observed in complex esters of o-substituted benzoic acid.

Scheme 2



The formation of the pyridine V proceeds, in all probability, in such a way that the tetrahydropyridine ring of II is opened and a new cyclization into dihydropyridine takes place (with separation of a molecule of formaldehyde) which is then oxidized to the pyridine V. The unusually facile breaking of a C—C bond in tetrahydropyridine apparently results from the presence of the two geminal electron-accepting substituents on the carbon atom in position 3.

EXPERIMENTAL

Infrared spectra were run on a UR-20 instrument in Nujol. Proton NMR spectra were obtained using a Bruker WH-90 (in DMSO-d_6 with TMS reference) and carbon-13 spectra on a Bruker WM 360 in $CDCl_3$ against cyclohexane. Mass spectra were run on an AEI MS-50 spectrometer, using direct introduction of the sample into the ion source with the ionization chamber at 250°C for compound II and 150°C for compound V, elemental composition was determined at a resolution ~60,000.

3,5-Diethoxycarbonyl-3-p-nitrobenzoyl-6-p-nitrophenyl-1,2,3,4-tetrahydropyridine (II). The ethyl ester of p-nitrobenzoylacetic acid (1.19 g, 5 mmoles), hexamethylenetetramine (1.05 g, 7.5 mmoles), and ammonium acetate (0195 g, 12 mmoles) were heated at boiling point in ethanol for 10 min. After cooling, the precipitate was recrystallized from ethanol. Yield, 0.4 g, 32%. Mp. 167-168°C. IR spectrum (in Nujol): 3320 (N—H), 1735 (C═O), 1689 cm^{-1} (C═O) (in chloroform): 3430 ((N—H), 1735 (C═O), 1690 cm^{-1} (C═O). ^1H NMR: 8.4-7.3 (8H, m, arom.), 7.14 (1H, t, J = 3.6 Hz, N—H), 4.19 (2H, q, J = 6.8 Hz, OCH_2CH_3), 3.62 (2H, q, J = 7.0 Hz, $OCH_2\mathbf{CH}_3$), 3.63 (2H, q, J = 12.2 Hz, 2-CH_2), 2.96 (2H, q, J = 16.2 Hz, 4-CH_2), 1.12 (3H, t, J = 6.8 Hz, $OCH_2\mathbf{CH}_3$), 0.68 ppm (3H, t, J = 7.0 Hz, $OCH_2\mathbf{CH}_3$). ^{13}C NMR 195.0 ($C_{(10)}$), 171.2 ($C_{(7)}$), 167.4 ($C_{(11)}$), 152.0 ($C_{(6)}$), 150.7 ($C_{(4'')}$), 148.6 ($C_{(4')}$), 145.6 ($C_{(1')}$), 141.2 ($C_{(1'')}$), 130.1 ($C_{(2'')}$), 129.9 ($C_{(2')}$), 124.5 ($C_{(3'')}$), 123.9 ($C_{(3')}$), 95.8 ($C_{(5)}$), 63.1 ($C_{(12)}$), 60.1, $C_{(8)}$), 56 ($C_{(3)}$), 47.5 ($C_{(2)}$), 30.7 ($C_{(4)}$), 14.4 ($C_{(9,13)}$). Mass spectra, m/z (%)*: 315 (15), 85 (13), 76 (13), 59 (11), 44 (22). Found: C 57.5, H 4.6, N 8.1%; M^+ 497.3032. Calculated for $C_{24}H_{23}N_3O_9$: C 58.0, H 4.6, N 8.4%, M 497.3015.

3-(α-Hydroxy-p-nitrobenzyl;-3,5-diethoxycarbonyl-6-p-nitrophenyl-1,2,3,4-tetrahydropyridine (III). Tetrahydropyridine (0.25 g, 0.5, mmoles) was dissolved in 50 ml methanol, 3 drops conc. hydrochloric acid added and then sodium borohydride (0.14 g, 2 mmoles) added in portions at room temperature. The mixture was left to stand overnight. It was then poured into water and the precipitate recrystallized from ethanol. Yield 0.1 g, 40%. mp 191-193°C. IR spectrum (in Nujol): 3460 (OH), 3360 (N—H), 1710 (C═O), 1650 cm^{-1} (C═O): (in chloroform): 3610 (OH), 3440 (N—H), 1728 (C═O), 1690 (cm^{-1} (C═O). Proton NMR: 8.2-7.2 (8H, m, arom.), 6.86 (1H, t, N—H), 6.14 (1H, d, j = 4.6 Hz, OH), 4.99 (1H, d, J = 4.6 Hz CH), 4.02 (2H, q, J = 6.8 Hz, $\mathbf{OCH}_2CH_3$), 3.66 (2H, q, J = 7.0 Hz, $\mathbf{OCH}_2CH_3$), 3.36 (2H, q, J = 12.6 Hz, 2-CH_2), 2.60 (2H, q, J = 12.4 Hz, 4-CH_2), 1.10 (3H, t, J = 6.8 Hz, $OCH_2\mathbf{CH}_3$), 0.7 ppm (3H, t, J = 7.0 Hz, $OCH_2\mathbf{CH}_3$). Found: C 55.4, H 4.8, N 8.7%. Calculated for $C_{24}H_{25}N_3O_9 \cdot H_2O$: C 55.7, H 5.3, N 8.1%.

3,5-Diethoxycarbonyl-3-p-nitrobenzoyl-1-nitroso-6-p-nitrophenyl-1,2,3,4-tetrahydropyridine (IV). Tetrahydropyridine II (0.25 g, 0.5 mmole) was dissolved in 10 ml glacial acetic acid and an excess of sodium nitrite (0.3 g) added in portions and boiled 5 min. The precipitated solid was recrystallized from ethanol. Yield 0.15 g (56%), mp 140°C. Gave positive

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*Ion peaks with intensities ≥10% are shown, not indicated in scheme 1.

Liebermann reaction for nitroso group. IR spectrum (in Nujol): 1734 (C=O), 1720 (C=O), 1700 cm^{-1} (C=O). Proton NMR: 8.4-7.5 (8H, m, arom.), 4.41 (2H, q, J = 12.4 Hz, 2-CH_2), 4.21 (2H, q, J = 6.8 Hz, $O\mathbf{CH_2}CH_3$), 3.82 (2H, q, J = 7.0 Hz, $O\mathbf{CH_2}CH_3$), 3.33 (2H, q, J = 12.4 Hz, 4-CH_2), 1.08 (3H, t, J = 6.8 Hz, $O\mathbf{CH_2}CH_3$), 0.73 ppm (3H, t, J = 7.0 Hz, $OCH_2\mathbf{CH_3}$). Carbon-13 NMR: 193.0 ($C_{(10)}$), 169.9 ($C_{(7)}$), 165.9 ($C_{(11)}$), 148.8 ($C_{(6)}$), 147.5 ($C_{(4'')}$), 145.8 ($C_{(4')}$), 141.2 ($C_{(1')}$), 139.9 ($C_{(1'')}$), 131.1 ($C_{(2')}$), 130.3 ($C_{(2'')}$), 126.9 ($C_{(3'')}$), 124.7 ($C_{(3')}$), 111.1 ($C_{(5)}$), 63.8 ($C_{(12)}$), 61.8 ($C_{(8)}$), 56.0 ($C_{(3)}$), 44.8 ($C_{(2)}$); 32.0 ($C_{(4)}$), 14.2 ($C_{(9)}$), 14.0 ($C_{(13)}$). Found: C 54.8, H 4.4, N 10.7%. Calculated for $C_{24}H_{22}N_4O_{10}$: C 54.8, H 4.2, N 10.6%.

3,5-Diethoxycarbonyl-2,6-di(p-nitrophenyl)pyridine (V). A. Tetrahydropyridine II (0.5 g, 1 mmole) was dissolved in 20 ml acetone containing 1 ml conc. hydrochloric acid and heated 1 h at bp. The solvent was distilled off and the residue treated with methanol and recrystallized from ethanol. Yield 0.3 g (65%), mp 195°C. IR spectrum (in chloroform) 1728 cm^{-1} (C=O). Proton NMR: 8.61 (1H, s, 4-H), 8.4-7.7 (8H, m, arom.), 4.43 (4H, q, $O\mathbf{CH_2}CH_3$), 1.11 (6H, t, $OCH_2\mathbf{CH_3}$). Carbon-13 NMR: 166.4 ($C_{(7)}$), 158.9 ($C_{(2)}$), 149.2 ($C_{(4')}$), 145.8 ($C_{(1')}$), 141.9 ($C_{(4)}$), 130.7 ($C_{(2')}$), 126.7 ($C_{(3)}$), 123.9 ($C_{(3')}$), 62.9 ($C_{(8)}$), 14.3 ($C_{(9)}$). Mass spectrum, m/z (%)*: 405 (9), 376 (9), 345 (6), 330 (9), 129 (24), 115 (18), 73 (71), 65 (47), 60 (100), 41 (94). Found: C 59.4, H 4.4, N 9.0%. Calculated for $C_{23}H_{19}N_3O_8$: C 59.4, H 4.2, N 8.9%.

B. A mixture of 0.1 g (0.2 mmole) tetrahydropyridine II and 0.05 g (0.2 mmole) chloranil was heated at bp for 1 h in 10 ml benzene. The solution was cooled and washed with cold 10% NaOH and with water. It was then dried over anhyd. sodium sulfate and the benzene evaporated. The residue was crystallized from petroleum ether. Yield 0.05 g (55%).

C. A mixture of 0.2 g (0.4 mmole) of tetrahydropyridine II and 0.55 g (5 mmole) selenium dioxide was heated at bp for 2 h in acetonitrile. The reaction mixture was poured into water and the product recrystallized from ethanol. Yield 0.05 g (25%).

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*Ion peaks with intensities $\geq 5\%$ are shown which are not shown in Scheme 2.

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