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Original Scientific Paper

Some Derivatives of Perhydro-imidazo(1,5-*a*)pyridine and Perhydro-pyrrolo(1,2-*c*)imidazole

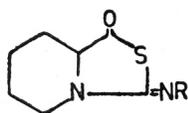
B. Stanovnik and M. Tišler

Department of Chemistry, University of Ljubljana, Ljubljana, Slovenia, Yugoslavia

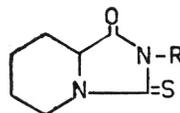
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Some derivatives of perhydro-imidazo(1,5-*a*)pyridine and -pyrrolo(1,2-*c*)imidazole were synthesized and a new synthetic route was also developed. This synthesis and other chemical and spectroscopical evidence indicates the structure for these substances with the *exo*-cyclic sulphur.

While investigating heterocyclic compounds containing thioamide groups, a paper was found wherein the authors¹ treated 2-carbethoxypiperidine with phenyl *iso*-thiocyanate in alcohol to obtain a product, to which the structure I ($R = C_6H_5$) was assigned. The other possible cyclic structure II ($R = C_6H_5$) was rejected as being less highly conjugated and as the compound was white, whereas most 2-thiohydantoin, closely related to structure II are yellow. Furthermore in the UV spectrum no absorption band was observed in the region at about 4000 Å in contrast to gliotoxin and related thiohydantoin² exhibiting this long wavelength absorption.

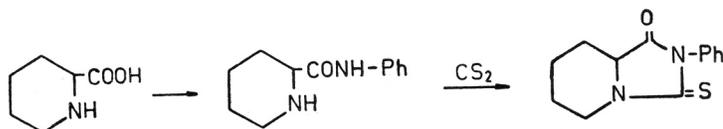


I



II

A re-examination of the above reaction with 2-carbethoxypiperidine and 2-carbethoxypyrrolidine with various *iso*-thiocyanates and a new synthetic approach to this class of substances revealed that the structure with the *exo*-cyclic sulphur is the correct one. The following synthesis was performed in the case of compound II ($R = C_6H_5$):

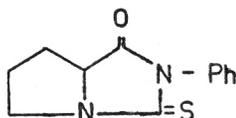


III

IV

Furthermore, all compounds we have prepared gave a positive iodine-azide reaction³, characteristic for the presence of a mercapto or thiocarbonyl group. The IR spectrum of IV and VI revealed no absorption in the 1690—1640 cm^{-1} region characteristic for the $-\text{N}=\text{C}-$ unsaturated system⁴, and to be expected for the other possible structure I. Also the UV spectra of both mentioned compounds were very similar when compared with that of the corresponding thiohydantoin and all compounds were lacking the absorption in the 3000—4000 Å region. An assignment of the thiocarbonyl stretching frequency was not attempted as this frequency is dependent on the structural environment and falls within the wide range 1400—1000 cm^{-1} ⁵.

When reacting 2-carbethoxypyrrolidine with phenyl *iso*-thiocyanate it was possible to isolate the uncyclized condensation product V which could be further transformed into the cyclic compound VI, also with an *exo*-cyclic sulphur.



VI

The thiocarbonyl sulphur is bound firmly and we were unable to convert the compound IV to the corresponding dioxo derivative by desulphurization with selenium dioxide⁶, hydrogen peroxide in pyridine or mercuric acetate. Severe reaction conditions caused decomposition and milder condition gave no reaction. The lack of reactivity in this instance is attributable to the increased stability of the thiohydantoin or hydantoin ring, observed particularly when both ring-nitrogens are substituted⁷.

EXPERIMENTAL

Melting-points were determined on a Kofler heating microscope. IR spectra were obtained on a Perkin-Elmer Model 21 Spectrophotometer, using a sodium chloride prism. The samples were examined as potassium bromide discs or as mulls in hexachlorobutadiene.

2-Carbethoxypyrrolidine was prepared according to the procedure of Kopfhammer and Matthes⁸.

2-Carbethoxypiperidine was made from 2-carboxypiperidine⁹ by the procedure of Reckhow and Tarbell¹.

TABLE I
2-Substituted 1-oxo-3-thio-perhydro-imidazo(1,5-a)pyridines (II)

R	M.p. °C	Formula	Analyses					
			Calc'd.		Found			
			%C	%H	%N	%C	%H	%N
<i>p</i> -Tolyl	144	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{OS}$	64.60	6.20	10.76	64.53	6.15	10.80
<i>o</i> -Chlorophenyl	139	$\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{OS}$	55.61	4.67	9.98	55.52	4.35	9.82
<i>m</i> -Chlorophenyl	158	$\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{OS}$	55.61	4.67	9.98	55.44	4.58	10.02
<i>p</i> -Chlorophenyl	169	$\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{OS}$	55.61	4.67	9.98	55.73	4.77	9.96

2-Substituted 1-oxo-3-thio-perhydro-imidazo(1,5-a)pyridines (Table I)

Ethanolic solutions of equimolecular amounts (1/300 mole) of 2-carbethoxy-piperidine and the corresponding *iso*-thiocyanates were refluxed for 15 min. For purification the compounds were crystallized from ethanol or aqueous ethanol. Yields 21—45%. In addition to this general procedure, compound II (R = C₆H₅) may be prepared also in a mixture of ethanol and hydrochloric acid.

2-Phenylcarbaminyl-piperidine (III)

To a stirred suspension of 5 g. of 2-carboxypiperidine hydrochloride in 50 ml. of acetyl chloride 5 g. of phosphorus pentachloride were added and, similar to a procedure of Ekenstam *et al.*¹⁰ reaction mixture was heated at 35° for 8 hr. while protected from moisture. Thereafter additional 2.5 g. of phosphorus pentachloride were added and heating continued at the same temperature for 6 hrs. The mixture was chilled on ice, filtered and the solid washed with dry toluene and acetone. The remaining acid chloride was suspended in 30 ml. of acetone, the stirred suspension treated with 7.0 g. of aniline and refluxed for 30 min. The cooled reaction mixture was filtered, washed with acetone to yield 3.5 g. of crude product as hydrochloride. This was dissolved in a small amount of water and made alkaline. The free base was filtered, washed with water and recrystallized from ethanol, yielding 2.5 g. (37%) of III, m.p. 80° (m.p. of the hydrochloride 262°).

Anal. C₁₂H₁₆N₂O (204.26) calc'd.: C 70.56; H 7.90; N 13.72%
found: C 70.64; H 8.18; N 13.85%

1-Oxo-2-phenyl-3-thio-perhydro-imidazo(1,5-a)pyridine (IV)

To a solution of 200 mg. (0.001 mole) of the compound III in 10 ml. of diethyl-ene glycol monoethyl ether, carbon disulphide (150 mg., 0.002 mole) and two drops of conc. aqueous ammonia were added. The mixture was heated on an oil bath (external temp. at the end about 150°) for 8 hrs. The solution was reduced *in vacuo* on a half of its volume and the residue poured into 20 ml. of water. The crude product (100 mg., 41%) was filtered and recrystallized twice from aqueous ethanol, m.p. 157°. The mixed m.p. with the compound, prepared according to Reckhow and Tarbell¹, showed no depression and the IR spectra were identical. The substance gave a positive iodine-azide reaction. UV spectrum (ethanol): λ_{max} 2705 Å, ε 15,500 and 2430 Å, ε 10,280. The IR spectrum exhibited the following important bands: at 1739 (assignable to CO group), 1504, 1449, 1379, 1319, 1307, 1209, 1130, 862, 740, and 694 cm⁻¹.

Anal. C₁₃H₁₄N₂OS (246.32) calc'd.: C 63.40; H 5.73; N 11.38%
found: C 63.64; H 5.52; N 11.22%

1-Phenylthiocarbaminyl-2-carbethoxy pyrrolidine (V)

An ethanolic solution of 2-carbethoxypyrrolidine (0.48 g.) was refluxed for 15 min. The colourless crystals (yield, 24%) were separated and recrystallized from aqueous ethanol, m.p. 125°. UV spectrum (ethanol): λ_{max} 2440 Å, ε 16,680.

Anal. C₁₄H₁₈N₂O₂S (278.36) calc'd.: C 60.42; H 6.52; N 10.07%
found: C 60.34; H 6.42; N 10.16%

1-Oxo-2-phenyl-3-thio-perhydro-pyrrolo(1,2-c)imidazole (VI)

An ethanolic solution of compound V (150 mg.) was refluxed for 1 hr. Yield: 90 mg. (72%). Upon recrystallization from ethanol the colourless crystals melted at 186°. UV spectrum (ethanol): λ_{max} 2710 Å, ε 15,130 and 2370 Å, ε 9,510.

Anal. C₁₂H₁₂N₂OS (232.29) calc'd.: C 62.06; H 5.21; N 12.06%
found: C 62.18; H 5.10; N 12.04%

2-Thio-3-phenyl-4-oxo-imidazoline (3-Phenyl-2-thiohydantoin) was prepared according to Aschan¹¹. UV spectrum (ethanol): λ_{max} 2660 Å, ε 14,980 and λ_{infl.} 2240 Å, ε 10,660.

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IZVOD

Derivati perhidro-imidazo(1,5-a)piridina i perhidro-pirol(1,2-c)imidazola

B. Stanovnik i M. Tišler

Opisana je sinteza nekih derivata perhidro-imidazo(1,5-a)piridina i -pirol(1,2-c)-imidazola kao i nov način sinteze. Sinteza i drugi kemijski i spektroskopski podaci daju dokaze za strukturu ovih spojeva sa egzocikličkim sumporom.

KEMIJSKI ODDELEK, FAKULTETA
ZA NARAVOSLOVJE IN TEHNOLOGIJO
UNIVERZE V LJUBLJANI

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