[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND BIOPHYSICS, UNIVERSITY OF CALIFORNIA]

Derivatives of 1-Methylisoquinoline

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Received January 23, 1961

In an attempt to prepare 1,1′,1″-triisoquinolylmethane (II) as a chelating agent for cuprous ion, 1-methylisoquinoline hydrochloride was allowed to react with 1-bromoisoquinoline. The product was not II nor the 1,1′-diisoquinolylmethane (I), but *N*-(1-isoquinolyl)-1-methylene-1,2-dihydroisoquinoline (III). 1-Carbethoxyisoquinoline reacted with 1-lithiumisoquinoline to give 1,1′-diisoquinolyl ketone (IV) in good yield. Reduction with sodium borohydride gave 1,1′-diisoquinolylcarbinol (V). A low yield of 1,1′,1″-triisoquinolylcarbinol (VI), was obtained by reaction of IV with 1-lithiumisoquinoline, but all attempts to reduce V and VI to the substituted methane proved unsuccessful.

This paper reports on attempted synthesis of 1,1′,1″-triisoquinolylmethane (II) which was desired as a possible chelator for cuprous ion. A preparation of the corresponding 2,2′,2″-triquinolylmethane was reported by Scheibe,[3] who heated together 2-methylquinoline and 2-chloroquinoline to obtain mixtures of 2,2′-diquinolylmethane and 2,2′,2″-triquinolylmethane. These compounds dissolved in concentrated sulfuric acid to produce an intense purple color. This color was explained by the addition of two protons of two of the nitrogens and loss of a proton from the central carbon to form the chromophore $-\overset{+}{\underset{H}{N}}=C-CH=C-\underset{H}{N}-$.

In this research, 1-bromoisoquinoline was heated with 1-methylisoquinoline to give a compound III which has the correct analysis and molecular weight for 1,1′-diisoquinolylmethane (I). The yield of compound III could be increased by using the hydrochloride of 1-methylisoquinoline, but no other product could be found under either reaction conditions. The great difference in melting point and solubility of compound III from the compounds obtained by Scheibe[3] suggested the reaction to have taken another course. Compound III could not be oxidized to 1,1′-diisoquinolyl ketone (IV) nor to its oxime by nitrosation, as Scheibe[3] observed for 2,2′-diisoquinolylmethane.

In the NMR spectrum no methylene hydrogen atoms were detected; all the peaks appeared to be in the aromatic region. The area determination yielded a value of approximately seven to eight hydrogen atoms per isoquinoline ring, based on the ratio of the hydrogen in 3 position to the total area of aromatic hydrogens. This suggested formula III in agreement with the analysis and the molecular weight findings. The fact that the ultraviolet spectrum is similar to that of isoquinoline and only showed a slight shift to larger wave lengths, was at first surprising. However, the *p*-orbital on the nitrogen of the isoquinoline ring may overlap with adjacent *p*-orbitals much as in isoquinoline and the spectrum of III might be expected to be similar to that of isoquinoline.

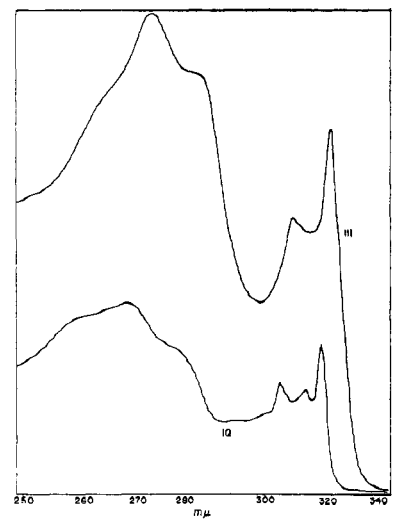

Fig. 1. Ultraviolet spectra of the reaction product of 1-bromoisoquinoline with 1-methylisoquinoline hydrochloride (III) and isoquinoline (IQ) in chloroform, $10^{-4}M$.

The presence of an exomethylene double bond suggested the possibility of an uptake of bromine. In fact, bromine in chloroform reacted very slowly to give an insoluble purple-red substance which was not characterized.

Oxidation with alkaline potassium permanganate[4] gave only phthalic acid, probably *via* hydroxyisoquinoline. No derivatives of pyridine-3,4-dicarboxylic acid, as expected for a preferable attack on the benzene ring in I, were found.

During the course of this investigation it was learned that 1,1′-diisoquinolylmethane[5] has been prepared by cyclization of malonyldi(β - phenylethyl)amide and subsequent oxidation to 1. This furthermore proved that III and I were not identical.

Another way which could lead to I and II was

(1) Trainee of USPHS 2G-119 training grant.

(2) We wish to acknowledge partial support by the American Cancer Society Grant P-218.

(3) (a) G. Scheibe and E. Rossner, *Ber.*, **53**, 2064 (1920); (b) G. Scheibe, *Ber*, **54**, 786 (1921); (c) G. Scheibe and G. Schmidt, *Ber.*, **55**, 3157 (1922).

(4) W. J. Gensler, *Heterocyclic Compounds*, Vol. IV, R. C. Elderfield, Ed., Wiley, New York, 1952, p. 405.

(5) T. N. Ghosh, S. K. Ganguly, and B. J. Bhattacharya, *Ind. Chem. Soc.*, **36**, 699 (1959).

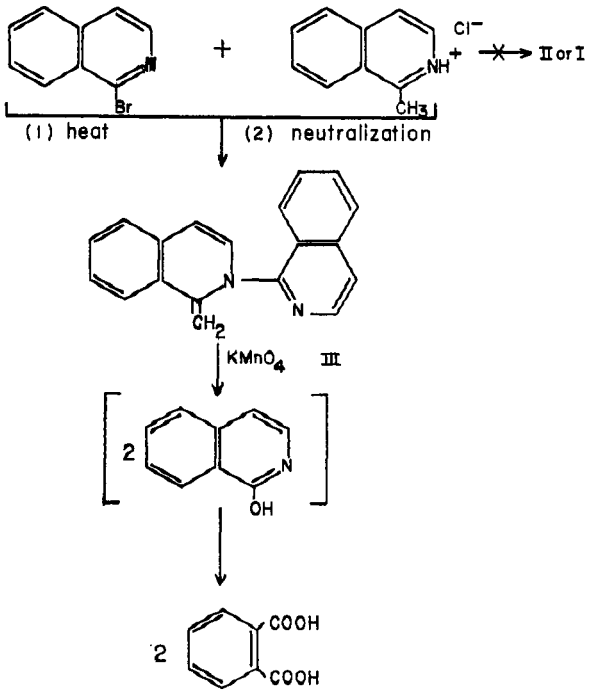

Figure 2

the reduction of 1,1′-di- and 1,1′,1″-triisoquinolylcarbinol (V and VI). 1,1′-Diisoquinolyl ketone (IV) was prepared in good yield by action of 1-lithium isoquinoline on 1-carbethoxyisoquinoline at −50°, a method applied by J. P. Wibaut *et al.*[6] in the pyridine series for preparing 2,2′-dipyridyl ketone and 2,2′,2″-tripyridylcarbinol. Attempts to reduce IV to I by the Wolff-Kishner method failed. Sodium borohydride reduced IV to 1,1′-diisoquinolylcarbinol (V). This carbinol could not be esterified with the usual reagents but it did react with phenyl isocyanate to give a urethane. When IV was allowed to react with 1-lithium isoquinoline in a mixture of ethyl ether and absolute pyridine, a small amount of 1,1′,1″-triisoquinolylcarbinol (VI) was obtained. The yield could not be improved, although unchanged IV was recovered. Phenyl isocyanate did not react with VI, which might be due to the protection of the hydroxy group by the aromatic rings surrounding the tertiary carbon atom. However, the spectroscopic evidence strongly supports the structure of VI. The ultraviolet spectra of V and VI are identical; the ratio of extinction at the maxima is about 2:3.

The infrared spectra shows an absorption at 2900 cm.$^{-1}$ in V due to the aliphatic hydrogen in the secondary carbinol group but missing in VI. The band for the hydroxy group appears at 3400 cm.$^{-1}$ in V but is displaced to 3230 cm.$^{-1}$ in VI. The various attempts to reduce the carbinols V and VI to the corresponding methanes I and II did not

(6) (a) J. P. Wibaut, A. P. De Jonge, H. G. P. Van der Voort, and P. Ph. H. L. Otto, *Rec. trav. chim.*, **70**, 1054 (1951). (b) J. P. Wibaut and P. Ph. H. L. Otto, *Rec. trav. chim.*, **77**, 1048 (1958).

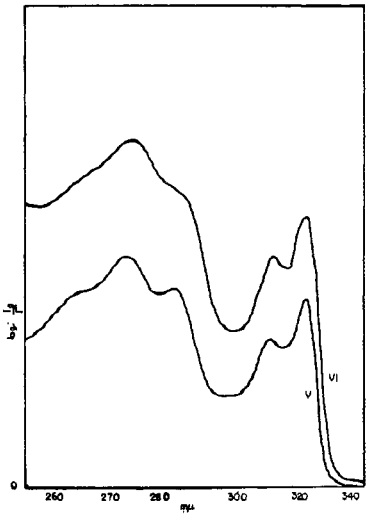

Fig. 3. Ultraviolet spectra 1,1′-diisoquinolylcarbinol (V), and 1,1′,1″-triisoquinolylcarbinol (VI) in chloroform, $5.10^{-5}M$.

furnish consistent results. Heating with 2-propanol and sulfuric acid, a method applied by P. D. Bartlett[7] for preparation of triphenylmethane from triphenylcarbinol, was not effective. Refluxing the carbinols with amalgamated zinc in hydrochloric acid on the contrary, yielded in both cases a deep red solution indicating that the chromophoric system —NH—C—C=C—NH— might have been formed. But on neutralization of the solution only

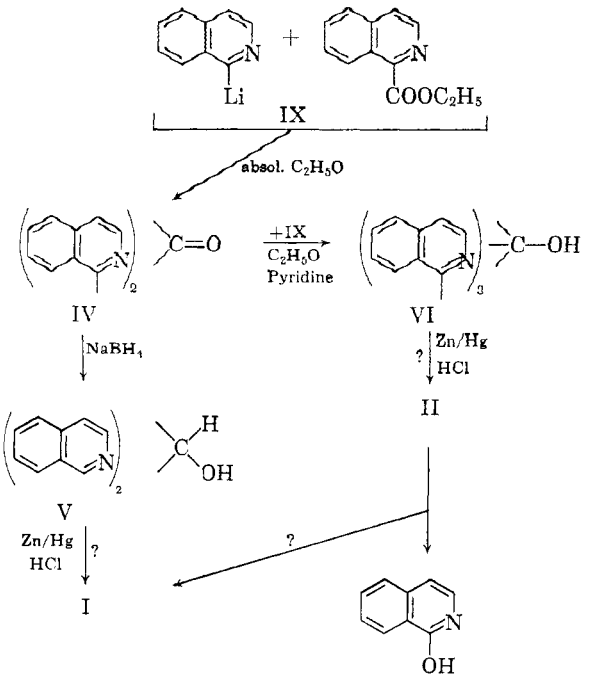

Figure 4

amorphous substances were obtained which could not be purified. In one case 1-hydroxyisoquinoline could be isolated from the reduction product of VI.

(7) P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Soc.*, **78**, 1441 (1956).

This indicates that II, had it been formed, underwent rapid "acid cleavage," like β-diketones, to hydroxyisoquinoline and I under the conditions applied. However, no I could be isolated from the reduction products of V or of VI.

EXPERIMENTAL

1-Hydroxyisoquinoline. In modification of Chichibabin's procedure [*Chem. Abstr.* 25, 2727 (1931)], 50 g. of freshly distilled isoquinoline and 100 g. of potassium hydroxide were placed in a 500-ml. stainless steel beaker fitted with an asbestos plate on top, holding a mechanical stirrer (stainless steel) and a glass tubing as reflux condenser, which ended in a drying tube. The potassium hydroxide was ground immediately before use. The beaker was placed in an oil bath and the mixture kept at 230° with continuous stirring until a sample taken out solidified completely on cooling. The reaction usually took about 5 hr. The hot product was mixed with ice and the hydrolysate filtered through a glass filter. The filtrate was neutralized and the precipitate filtered. The combined solids were washed several times with water, then with a small amount of alcohol, and eventually recrystallized from dioxane with aid of charcoal. A yield of 20–30 g. of slightly brownish needles, m.p. 209°, was obtained by this procedure.

1-Bromoisoquinoline was prepared by action of phosphorous tribromide on 1-hydroxy-isoquinoline according to J. P. Wibaut,[8] *1-methylisoquinoline* according to V. Boekelheide and J. Weinstock[9] and *1-carbethoxyisoquinoline* according to J. J. Padbury and H. G. Lindwall.[10]

Reaction of 1-methylisoquinoline with 1-bromiosoquinoline. A mixture of 11 g. of 1-methylisoquinoline hydrochloride, prepared by passing hydrogen chloride gas through an alcoholic solution of the base, and 11 g. of 1-bromoisoquinoline was placed into five test tubes of 1/2 × 4 in. and the tubes were sealed. They were slowly heated in a paraffin bath to 150°. At this temperature the reaction started with the formation of a red color. The tubes were occasionally shaken. When the mixture became a homogeneous solution the temperature was raised to 220° and kept there until the contents solidified to a dark red crystalline mass. The tubes were cooled and then opened. The contents were hydrolyzed in cold water overnight. The insoluble part was taken up in dilute sulfuric acid. On neutralization, the combined red solutions precipitated a brown, sometimes a violet, solid, which was recrystallized from chloroform. A 44% yield (6.26 g.) of white crystals was obtained, m.p., 289–291°. The substance is very slightly soluble in alcohol, carbon tetrachloride, and benzene; it dissolves in acids with a red color, which is less intense in concentrated acids.

Anal. Calcd. for $C_{19}H_{14}N_2$: mol. wt., 270.3; C, 84.42; H, 5.22; N, 10.61. Found: mol. wt., (Rast) 274, 264, 261; C, 84.41; H, 4.65; N, 10.78.

Oxidative degradation of III. A solution of 16 g. of potassium permanganate and 35 ml. of saturated sodium carbonate in 1000 ml. of water was gradually added to 2.7 g. of III in 100 ml. of 3% sulfuric acid under reflux. The immediate decolorization of potassium permanganate ceased after most of it had been added. An additional 4 g. of potassium permanganate was added and the mixture allowed to stand overnight. The excess of oxidant was reduced with methanol; the manganese dioxide was to stand overnight. The excess of oxidant was reduced with methanol; the manganese dioxide was filtered and extracted by boiling with water. The combined solutions were evaporated and the residue was taken up in alcohol, filtered, evaporated, taken up in alcohol again, and evaporated to dryness. The residue was extracted with chloroform. The residue obtained on evaporation (1 g.) was sublimed *in vacuo*. The sublimate consisted of white needles, m.p. 124°. The melting point was undepressed by mixing with an authentic sample of phthalic anhydride, prepared by vacuum sublimation of phthalic acid.

Reaction of III *with bromine.* A solution of bromine in chloroform was added to 80 mg. of III dissolved in a minimum of chloroform. After 2 days of standing, dark red needles had precipitated (250 mg.), which decomposed at 250° and were insoluble in cold alcohol and water.

1,1'-Diisoquinolylketone (IV). The butyllithium prepared according to Gilman[11] was used in an excess of 1.25 mole per mole of the compound being metalated, since the titration of butyllithium showed a yield of 80% immediately after preparation.

A solution of 24 g. of 1-bromoisoquinoline (0.113 mole) in 50 ml. of absolute ether was run into a solution of *n*-butyllithium, prepared from 19.5 g. of *n*-butyl bromide and 2.0 g. of lithium in 200 ml. of absolute ether, at −60° bath temperature. A green color appeared which after a while changed to brown. The mixture was stirred for 0.5 hr. and 28.5 g. of 1-carbethoxyisoquinoline (0.113 mole), dissolved in a small amount of ether, was slowly added at −60° while stirring was continued. A greenish precipitate formed, which changed to light brown on raising the temperature to 20°. After 3 hr. water was slowly added. On acidification with dilute sulfuric acid the yellow solid partially dissolved. The remaining solid was separated and dissolved in 18*N* sulfuric acid, the solution being combined with the acid layer obtained before. The remaining other layer was extracted once more with 18*N* sulfuric acid, the acid solution neutralized and the oily product washed with little alcohol. The white substance thus obtained (0.54 g.) melted at 155–157° and was identical with 1-carboxyisoquinoline. The acid solution containing the main product was neutralized and the precipitate recrystallized from *n*-butyl alcohol; total yield, 61%, m.p. 199–200°. The compound is not soluble in ether.

Anal. Calcd. for $C_{19}H_{12}ON_2$: C, 80.26; H, 4.26, N, 9.86. Found: C, 80.35, H, 4.24; N, 9.67.

Oxime of IV. To 0.5 g. of the ketone dissolved in absolute pyridine was added 0.5 g. hydroxylamine hydrochloride. After 2 days of standing the pyridine was distilled *in vacuo*, the residue taken up in water and the insoluble mass recrystallized from alcohol water, m.p. 260° dec.

Anal. Calcd. for $C_{19}H_{13}ON_3$: N, 14.04. Found: N, 14.21.

1,1'-Diisoquinolylcarbinol (V). A solution of 3 g. of the ketone described above (0.01 mole) in 50 ml. of absolute dioxane was placed in a three necked flask equipped with stirrer and dropping funnel. A solution of 0.1 g. of sodium borohydride (0.0025 mole) plus a slight excess in alcohol was added slowly during stirring. The addition was followed by the appearance of an intensive blue color which changed to yellow immediately. If after addition of all the reducing agent, a sample taken out did not evolve hydrogen on addition of acid, sodium borohydride was added. After 3 hr. the solution was hydrolyzed with dilute sulfuric acid. The precipitate which formed was filtered and dissolved in more sulfuric acid. Precipitation with aqueous ammonia yielded a pink substance. It was recrystallized from carbon tetrachloride, whereupon 2.2 g. of the carbinol V was obtained as white crystals, m.p. 173–175°; yield, 73%.

Anal. Calcd. for $C_{19}H_{14}ON_2$: C, 79.69; H, 4.93; N, 9.78. Found: C, 79.83; H, 5.11; N, 9.63.

Phenylurethane. A solution of 0.5 g. of V and 0.21 g. of phenylisocyanate (both 1.75 mmoles) in absolute dioxane was refluxed for 1 day. On hydrolysis 0.45 g. of a solid substance was obtained, m.p. 202° after recrystallization from butanol.

Anal. Calcd. for $C_{26}H_{19}O_2N_3$: C, 77.30; H, 4.83; N, 10.35. Found: C, 77.01; H, 4.72; N, 10.37.

1,1',1''-Triisoquinolylcarbinol (VI). A solution of 10.2 g.

(8) J. P. Wibaut, *Rec. Trav.*, 62, 466 (1943).

(9) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, 74, 660 (1952).

(10) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.* 67, 1268 (1945).

(11) H. Gilman, *Org. Reactions*, VIII, 285 (1928).

of 1-bromoisoquinoline (0.05 mole), in 50 ml. of absolute ether, was run into a solution on *n*-butyllithium, prepared from 8.4 g. of butyl bromide and 0.87 g. of lithium in 100 ml. ether, at −60° bath temperature. After the addition, the mixture was stirred for 0.5 hr. at −60° and then a solution of 14 g. of 1,1′-diisoquinolyl ketone (IV, 0.05 mole) in 150 ml. of absolute pyridine was added gradually at −60°. (The ketone precipitated after dissolving in hot pyridine in fine crystals. The rest of the suspension was therefore rinsed out of the dropping funnel with more pyridine into the reaction flask.) The mixture was stirred vigorously at −60° for 2 hr., then it was allowed to warm up to room temperature and was stirred for another 5 hr.

The dirty green mixture was acidified with aqueous sulfuric acid. The insoluble material was filtered and dissolved in 18*N* sulfuric acid. The acid solutions were combined and neutralized. The precipitate was washed with petroleum and then boiled with alcohol. The extract yielded 2.60 g. of the original ketone, including the recoveries from the mother liquor. The alcohol insoluble part was boiled with 300 ml. of butanol, whereupon 1.35 g. of VI was obtained from the solution; the mother liquor yielded 2.05 g. of IV. The solid residue of the butanol was taken up in 300 ml. of butanol again and dissolved by refluxing. An additional 2.85 g. of VI was obtained on cooling the solution and working up the mother liquor. Recovery of the ketone was 4.65 g., 33%. Total yield of carbinol 4.20 g., 20%, m.p. 244–245°.

Anal. Calcd. for $C_{28}H_{19}ON_3$: C, 81.26; H, 4.74; N, 10.02. Found: C, 81.34; H, 4.63; N, 10.16.

Reduction with zinc amalgam. A solution of 250 mg. of the carbinol in 15 ml. of 4*N* hydrochloric acid was reluxed for 1 hr. with amalgamated zinc turnings. A red solution was obtained which precipitated a brownish matter on neutralizing with ammonia. The product was taken up in chloroform, the solution dried and concentrated. On standing, crystals appeared; the amount was increased on adding carbon tetrachloride. Recrystallization from carbon tetrachloride-petroleum ether (b.p. 100–115°) gave crystals, m.p. 212°. On mixing with an authentic sample of 1-hydroxyisoquinoline no depression of the melting point was observed. The ultraviolet spectrum was identical with that of the hydroxyisoquinoline.

Acknowledgment. We wish to thank Dr. R. E. Lundin from the U. S. Department of Agriculture, 800 Buchanan Street, Albany, Calif., for the investigation and explanation of the NMR spectra.

DAVIS, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOFFMANN-LA ROCHE INC.]

Quinazolines and 1,4-Benzodiazepines. IV.[1,2] Transformations of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide[3]

L. H. STERNBACH AND E. REEDER

Received June 19, 1961

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (I) and its acetyl derivative (II) can be hydrolyzed to 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III). Other methods are described for the synthesis of this compound and its conversion into pharmacologically active benzodiazepinones.

The interesting finding that 7-chloro-2-methylamino-5-phenyl-3H,1,4-benzodiazepine 4-oxide (I)[4] hydrochloride and its acetyl derivative, 7-chloro-2-(*N*-methyl-acetamido)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II), showed very similar muscle relaxant, sedative, and anticonvulsant properties in animals suggested that these two compounds owed their activity to a common degradation product.

In the search for such a product the decomposition of II was studied. Treatment with alkali resulted in its reconversion into I[5]; however, hydrolysis with dilute mineral acid at room temperature gave an almost quantitative yield of a degradation product (III)[6] which was pharmacologically[4] very similar to the starting material. The same compound was also formed on prolonged standing of an aqueous solution of the hydrochloride of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.[7]

The composition and genesis indicated for this degradation product the structure III. This was confirmed by the infrared spectrum (0.3% solution in chloroform) showing a strong carbonyl band at 1706 cm.$^{-1}$, and an NH hydrogen band at 3400 cm.$^{-1}$

Additional evidence was supplied by the chemical behavior of the compound. It had acidic properties which can be attributed to the electron withdrawing properties of the *N*-oxide oxygen. It was soluble in 1*N* alkali and recovered unchanged on acidification. On prolonged treatment with an excess of alkali the amide linkage was split and an amino acid (VIII) was formed which could be reconverted into the lactam III by heating or prolonged treatment with

(1) Paper III of this series, L. H. Sternbach, E. Reeder, O. Keller, W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

(2) Presented in part at the Gordon Research Conference, Medicinal Chemistry Section, August 1961.

(3) Marketed under the trade name Librium®.

(4) The pharmacological investigations were done by Dr. L. O. Randall and his co-workers and will be published elsewhere.

(5) Paper II of this series, L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(6) In addition *N*-methylacetamide was formed, which proved the position of the acetyl group on the exocyclic nitrogen atom.

(7) B. A. Koechlin and M. A. Schwartz (Federation Proceedings Vol. 20, Part 1, 171, March 1961) later found this degradation product (III) also in the blood and urine of Librium® treated people and animals. It has, however, not yet been established whether the biological activity of Librium® is due to conversion into this compound.