SYNTHESIS OF 1,2,4-TRIAZINO[5,6-*b*]- AND IMIDAZO[4,5-*b*]QUINOLINE DERIVATIVES*

Jan SLOUKA[a], Vojtěch BEKÁREK[a], Karel NÁLEPA[a] and Antonín LYČKA[b]

[a] *Department of Analytical and Organic Chemistry, Palacký University, 771 46 Olomouc and*
[b] *Research Institute of Organic Syntheses, 532 18 Pardubice - Rybitví*

Received January 11th, 1984

o-Nitrophenylpyruvic acid thiosemicarbazone (*I*) has been cyclized to 2-thio-5-(*o*-nitrobenzyl)-6-azauracil (*II*) which has been transformed in 5-(*o*-nitrobenzyl)-6-azauracil (*III*) by both oxidation, and methylation and hydrolysis of the 3-methylmercapto-6-(*o*-nitrobenzyl)-2,5-dihydro-1,2,4-triazin-5-one (*V*) formed. Reduction of derivative *III* with iron(II) hydroxide and cyclization of the amino derivative *IV* formed gives 2,3,4,10-tetrahydro-1,2,4-triazino[5,6-*b*]quinolin-3-one (*VI*). Compound *VI* is transformed in acid medium to 1-amino-1,2-dihydroimidazo-[4,5-*b*]quinolin-2-one (*VIII*) *via* the tautomer *VII*, and in boiling acetic acid it gives the acetylamino derivative *IX*. The N-amino derivative *VIII* reacts with carbonyl compounds to give the corresponding hydrazones *X*—*XII*, and its nitrosation gives 1,2-dihydroimidazo[4,5-*b*]-quinolin-2-one (*XIII*).

A series of condensed 1,2,4-triazines were advantageously prepared by intramolecular condensation reactions of carbonyl group of the 6-azauracil cycle. This reaction class includes the syntheses of 1,2,4-triazino[2,3-*a*]quinazoline derivatives[1] and 1,2,4-triazino[2,3-*a*]benzimidazole derivatives[2] which consist in an intramolecular condensation of 2-carbonyl group of 6-azauracil with amino group. Analogous intramolecular condensations of 4-carbonyl group of 6-azauracil cycle were used for syntheses of 1,2,4-triazino[5,6-*b*]indole derivatives[3,4], 1,2,4-triazino[5,6-*c*]cinnoline derivatives[5] and 1,2,4-triazino[5,6-*c*]isoquinoline derivatives[6]. Hajpál and Berényi[7] described an analogous cyclization of 5-(*o*-aminobenzyl)-6-azauracil leading to 2,3,4,10-tetrahydro-1,2,4-triazino[5,6-*b*]quinolin-3-one. The starting 5-(*o*-aminobenzyl)-6-azauracil was prepared by the same authors[8] *via* cyclization of *Z*-form of *o*-nitrophenylpyruvic acid semicarbazone and catalytic hydrogenation of the 5-(*o*-nitrobenzyl)-6-azauracil formed.

The present communication deals with an easier method of preparation of the said derivative of 1,2,4-triazino[5,6-*b*]quinoline and investigates its transformation to imidazo[4,5-*b*]imidazole derivatives.

In contrast to the authors[8] we started from *o*-nitrophenylpyruvic acid thioseme-

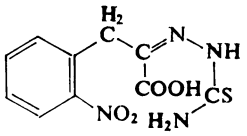
* Part IX in the series on 5-Substituted 6-Azauracils; Part VIII: Pharmazie *39*, 186 (1984).

carbazone (*I*) whose alkaline cyclization to the corresponding 2-thio-5-(*o*-nitrobenzyl)-6-azauracil (*II*) proceeds smoothly, and it is not necessary to isolate the *Z*-form of the thiosemicarbazone (which must be done in the case of the analogous semicarbazone). The starting thiosemicarbazone (*I*) was obtained (besides the reaction of *o*-nitrophenylpyruvic acid with thiosemicarbazide) by more advantageous azlactone method[9] starting from 2-methyl-4-(*o*-nitrobenzylidene)-2-oxazolin-5-one. The thio derivative *II* was transformed to 5-(*o*-nitrobenzyl)-6-azauracil (*III*) by both oxidation with permanganate and methylation to 3-methylmercapto-2,5-dihydro-6-(*o*-nitrobenzyl)-1,2,4-triazin-5-one (*V*) and subsequent acid hydrolysis. The derivative *III* prepared by the two methods is identical with the substance obtained by Hajpál and Berényi[8] (*via* cyclization of the *Z*-form of *o*-nitrophenylpyruvic acid semicarbazone). In the IR spectrum of this compound we identified the bands of valence vibrations of N—H bonds (3 320 and 3 143 cm^{-1}), both carbonyl groups (1 715 and 1 670 cm^{-1}), and nitro group (1 524 and 1 338 cm^{-1}). The band at lower wave number was assigned to 2-carbonyl group of 6-azauracil cycle. The IR spectrum of the 2-thio derivative *II* differs from the previous one especially in that there is only one band of carbonyl group present (1 688 cm^{-1}), and an intense band of thiocarbonyl group is found at 1 217 cm^{-1}. The nitro group of this derivative is manifested by two bands of valence vibrations at 1 513 and 1 343 cm^{-1}. The IR spectrum of the methylmercapto derivative *V* differs from that of *II* first of all by the absence of the band of thiocarbonyl group and by a shift of the band of valence vibration of carbonyl group to the value of 1 640 cm^{-1}.

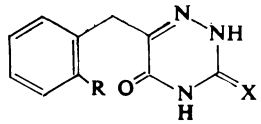
The selective reduction of nitro derivative *III* was achieved by application of iron(II) hydroxide in weak alkaline medium. The formed raw 5-(*o*-aminobenzyl)-6-azauracil (*IV*) was (without further purification) cyclized to 2,3,4,10-tetrahydro-1,2,4-triazino-[5,6-*b*]quinolin-3-one (*VI*) in good yields by boiling in ethanol in the presence of acetic acid. The given tautomeric structure of compound *VI* was determined[7] from IR and ^{1}H NMR spectra and confirmed by our results (IR, ^{1}H NMR, and ^{13}C NMR). In the proton-decoupled ^{13}C NMR spectrum of compound *VI* we found 10 signals in accordance with the constitution, the signal of the carbon atom of 10-CH_2 group being found at 29·77 ppm.

The tautomeric structure *VI* lacks a fully aromatic quinoline system, hence it can be expected to be easily tautomerized into *VII* (which contains such aromatic system). However, heating of compound *VI* in hydrochloric acid gave the isomeric 1-amino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*VIII*) instead of the tautomer *VII* (1,2,3,4-tetrahydro-1,2,4-triazino[5,6-*b*]quinolin-3-one), due obviously to easy transformation *VII*→*VIII* at these conditions. Nevertheless, we found that ring contraction of 1,2,4-triazine cycle takes place in slightly acidic medium, too, as it follows from the fact that longer heating in anhydrous acetic acid transforms the derivative *VI* into 1-acetylamino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*IX*) in good yields.

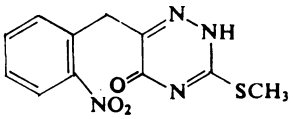
This transformation proceeds either *via* the acetyl derivative of the *VII* tautomer which undergoes the ring contraction, or – more probably – *via* the *VIII* derivative whose amino group undergoes acetylation under the conditions given. The later variant is supported by the easy acetylation *VIII*→*IX* accomplished by boiling the N-amino derivative in acetic acid. The preparation of compounds *VIII* and *IX* does not need to start from the derivative *VI*, but the same result is obtained when using the raw amino derivative *IV* which produces compound *VI* as an intermediate at the reaction conditions given.



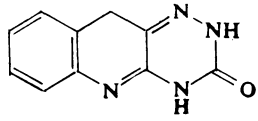
I



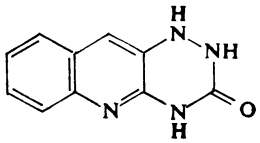
II, R = NO_2, X = S
III, R = NO_2, X = O
IV, R = NH_2, X = O



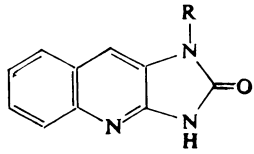
V



VI



VII



VIII, R = $-NH_2$
IX, R = $-NH-CO-CH_3$
X, R = $-N=CH-C_6H_5$
XI, R = $-N=CH-C_6H_4-NO_2$-(4)
XII, R = $-N=CH-C_6H_4-NO_2$-(4)
XIII, R = $-H$

Structure of compounds *VIII* and *IX* was confirmed by IR and NMR spectroscopy. The N-amino derivative *VIII* shows two intense bands of N—H valence vibrations at 3 292 and 3 180 cm^{-1} and an intense band of valence vibration of carbonyl group at 1 711 cm^{-1}. When compared with the isomeric compound *VI*, the band of the valence vibration is shifted to higher wave numbers due to the carbonyl carbon

atom being a member of the only five-membered cycle. Also the results of ^{1}H NMR and ^{15}N NMR spectroscopy support the N-amino structure *VIII* and exclude the structures *VI* and *VII* which contain three N-H groups each. The ^{1}H NMR spectrum shows a broad singlet at 6·20 ppm (2 H intensity) and the proton-decoupled ^{15}N NMR spectrum (natural abundance of the ^{15}N isotope) shows only two signals with chemical shifts −256·5 ppm (NH) and −324·7 ppm (NH_2). It is reasonable to suppose that under used experimental conditions (proton noise decoupling and 5 s pulse repetition time) these signals are due to nitrogen atoms carrying hydrogen. A comparison with published data[13] on ^{15}N NMR chemical shifts of NH and NH_2 groups allows to assign these signals to the NH (−256·5 ppm) and NH_2 (−324·7 ppm) groups. An attempt to obtain ^{15}N NMR chemical shifts of the other nitrogen atoms has not been successfull even with the use of $Cr(acac)_3$ as a relaxation agent because of small solubility of compound *VIII* even at higher temperatures. The IR spectrum of the acetyl derivative *IX* exhibits two bands of valence vibrations of carbonyl groups at 1 702 and 1 723 cm^{-1}. The structure of this compound also follows from its easy hydrolysis to the N-amino derivative *VIII*.

The N-amino group of compound *VIII* shows all typical reactions of hydrazine. Besides its above-mentioned easy acylation (to give the derivative *IX*), compound *VIII* is easily condensed with carbonyl compounds (as *e.g.* benzaldehyde or its *p*-nitro or *p*-chloro derivatives) to give the corresponding hydrazones *X*–*XII*. Also nitrosation has a course typical of N-amino compounds: after splitting off of N_2O the reaction gives smoothly 1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*XIII*).

EXPERIMENTAL

The melting points were determined with a Boetius apparatus and are not corrected. The IR spectra were measured by the KBr technique with an IR-75 (Zeiss, Jena) apparatus. ^{1}H, ^{13}C and ^{15}N NMR spectra were measured by standard way with JNM-FX 100 (JEOL) spectrometer at 99·602 (^{1}H), 25·047 (^{13}C) and 10·095 (^{15}N) MHz in hexadeuteriodimethyl sulphoxide with tetramethylsilane as an internal standard (^{1}H and ^{13}C NMR) and external neat $CH_3{}^{15}NO_2$ (25% ^{15}N enrichment) in the case of ^{15}N NMR spectra. The positive value means shifts to lower fields.

o-Nitrophenylpyruvic Acid Thiosemicarbazone (*I*)

a) A mixture of 4·20 g (20·1 mmol) *o*-nitrophenylpyruvic acid[11] and 1·80 g (19·7 mmol) thiosemicarbazide in 250 ml water was shortly boiled and cooled. After standing overnight, the product was collected by suction, washed with water, and dried. Yield 4·72 g (85%), m.p. 187 to 189°C (ethanol–water).

b) A mixture of 9·30 g (40·0 mmol) 2-methyl-4-(*o*-nitrobenzylidene)-2-oxazolin-5-one[10], 15 ml 37% HCl, and 100 ml water was refluxed 2·5 h. After addition of 3·80 g (41·7 mmol) thiosemicarbazide, the mixture was shortly boiled, 13 g sodium acetate (anhydrous) was added, and the mixture was cooled. After standing overnight, the product was collected by suction, washed with water and dried. Yield 8·95 g (79%), m.p. 187–189°C (aqueous ethanol). For $C_{10}H_{10}N_4O_4S$ (282·2) calculated: 42·56% C, 3·57% H, 19·85% N; found: 42·43% C, 3·72% H, 19·97% N.

2-Thio-5-(*o*-nitrobenzyl)-6-azauracil (*II*)

A mixture of 7·10 g (25·2 mmol) thiosemicarbazone *I*, 4·0 g Na_2CO_3, and 100 ml water was boiled 4 h, filtered with little charcoal, and acidified with HCl (pH 1). After several hours, the separated crystalline solid was collected by suction, washed with water, and dried at 120°C. Yield 5·76 g (87%), m.p. 198—200°C (aqueous ethanol). For $C_{10}H_8N_4O_3S$ (264·2) calculated: 45·46% C, 3·05% H, 21·21% N; found: 45·70% C, 2·87% H, 21·14% N. IR spectrum (KBr, cm^{-1}): 1 217 (ν(C=S), 1 343, 1 513 ($\nu(NO_2)$), 1 688 (ν(C=O).)

5-(*o*-Nitrobenzyl)-6-azauracil (*III*)

a) A mixture of 5·30 g (20·1 mmol) compound *II*, 4·00 g Na_2CO_3, and 130 ml water was heated until dissolution. The solution was then treated with 6·40 g (40·5 mmol) $KMnO_4$ in 330 ml warm water which was added drop by drop at 40—50°C during 1 h. The mixture was stirred 1 h, treated with 3—5 ml methanol, and filtered. The precipitate of MnO_2 was washed with hot water and suspended in 150 ml hot water, and filtered again. The combined filtrates and washing water were filtered with little charcoal, acidified with hydrochloric acid (pH 0), and shortly boiled. After standing overnight, the crystalline precipitate was collected by suction, washed with water, and dried at 130°C. Yield 3·85 g (77%), m.p. 210—212°C (aqueous ethanol); ref.[8] gives m.p. 211—212°C.

b) A mixture of 3·60 g (12·9 mmol) derivative *V*, 60 ml 37% HCl, and 30 ml 96% ethanol was refluxed 4 h and cooled. After standing overnight. the crystalline precipitate was collected by suction, washed with water, and dried at 130°C. Yield 2·40 g (75%), m.p. 210—212°C (aqueous ethanol). IR spectrum (KBr, cm^{-1}): 1 338, 1 524 ($\nu(NO_2)$), 1 670, 1 715 (ν(C=O)), 3 143, 3 320 (ν(N—H)).

3-Methylmercapto-6-(*o*-nitrobenzyl)-2,5-dihydro-1,2,4-triazin-5-one (*V*)

A solution of 3·00 g (11·4 mmol) compound *II* and 2·30 g KOH in 230 ml water was treated with 0·75 ml (12·0 mmol) methyl iodide. The mixture was stirred in a closed flask at room temperature 2 h, after 48 h it was filtered, and acidified with hydrochloric acid (pH 1). The crystalline precipitate was collected by suction, washed with water, and dried at 120°C. Yield 2·40 g (76%), m.p. 199—200°C (aqueous ethanol). For $C_{11}H_{10}N_4O_3S$ (178·2) calculated: 47·48% C, 3·62% H, 20·14% N; found: 47·58% C, 3·57% H, 20·00% N. IR spectrum (KBr, cm^{-1}): 1 640 (ν(C=O)).

2,3,4,10-Tetrahydro-1,2,4-triazino[5,6-*b*]quinolin-3-one (*VI*)

A solution of 50·50 g (160·1 mmol) $Ba(OH)_2.8\ H_2O$ in 350 warm water was added to a solution of 44·50 g (160·1 mmol) $FeSO_4.7\ H_2O$ in 150 ml water with stirring. The suspension formed was heated at 40°C, and a solution of 5·00 g (20·15 mmol) nitroderivative *III* and 4·0 ml 25% NH_3 in 80 ml water was added thereto with intensive stirring. The reaction temperature increased to about 45°C and was maintained 1 h, whereupon the reaction mixture was heated on boiling water bath 1 h. The precipitated solid was collected by suction, washed with 3 × 100 ml hot water, mixed with 400 ml hot water and 1·5 ml 25% NH_3, filtered again, and washed with 2 × × 50 ml hot water. The combined filtrates and washing water were filtered with little charcoal and evaporated in vacuum. The evaporation residue (4·45 g raw derivative *IV*) was mixed with 320 ml ethanol and 15 ml acetic acid, and the mixture was refluxed 1 h. Then it was filtered with little charcoal, concentrated to about one third of its original volume, and diluted with about 30 ml water. After standing overnight, the yellow crystalline solid was collected by suction, washed with little ethanol, and dried at 150°C. Yield 3·21 g (80%). After recrystallization from

ethanol, the substance decomposes above 258°C without melting until 360°C. Ref.[7] gives m.p. 259–261°C. IR spectrum (KBr, cm^{-1}): 1 668 s, 1 630 s, 1 463 s, 1 445 s, 1 409 s (ν(C=O), ν(C=N), ν(C=C)), 3 135 m, 3 220 sh ((N—H)). ^{1}H NMR spectrum (δ, ppm): 4·08 (2 H, singlet, CH_2), 7·04–7·38 (4 H, multiplet, aromatic CH), 10·80 (1 H, singlet, NH) and, 1220 (1 H, singlet, NH). ^{13}C NMR (proton-decoupled) spectrum (δ, ppm): 29·77 (CH_2), 116·00, 119·22, 123·20, 127·51, 128·87, 131·51, 135·60, 153·80, 154·90.

1-Amino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*VIII*)

a) A mixture of 200 mg (1·0 mmol) triazine *VI*, 50 ml water, and 1·0 ml 37% HCl was refluxed 2·5 h and evaporated. The evaporation residue represents *VIII*.HCl (yield 237 mg, 100%); for $C_{10}H_9ClN_4O$ (236·7) calculated: 50·75% C, 3·83% H, 23·68% N; found: 50·52% C, 3·76% H, 23·72% N. The product was mixed with 5 ml water and 80 mg CH_3CO_2Na. After several hours, the crystalline solid was collected by suction, washed with water, and dried at 140°C. Yield 185 mg (92%), m.p. 301–303°C decomp. (ethanol).

b) A mixture of 220 mg (1·00 mmol) raw amino derivative *IV*, 50 ml water, and 1·0 ml 37% HCl was refluxed 2·5 h and further treated as sub *a*). Yield 170 mg (77%). After recrystallization from ethanol the product obtained is identical with the previous one.

c) A mixture of 245 mg (1·0 mmol) acetyl derivative *IX*, 12 ml water, and 3·0 ml 37% HCl was refluxed 1 h and treated further as sub *a*) and *b*). Yield 193 mg (95%). After recrystallization from ethanol the product obtained is identical with that prepared above (*a*, *b*). For $C_{10}H_8N_4O$ (200·2) calculated: 59·99% C, 4·03% H, 27·99% N; found: 60·00% C, 3·96% H, 28·13% N. IR spectrum (KBr, cm^{-1}): 1 711 s (ν(C=O)), 3 180, 3 292 (ν(N—H)). ^{1}H NMR spectrum (δ, ppm): 7·4–8·0 (5 H, multiplet). ^{15}N NMR spectrum (at the natural ^{15}N isotope level with the proton-decoupling, δ, ppm): −256·5 (singlet NH), −324·7 (singlet NH_2).

1-Acetylamino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*IX*)

a) A mixture of 400 mg (2·0 mmol) triazine *VI* and 30 ml acetic acid was refluxed 10 h, filtered with little charcoal, and the filtrate was concentrated to a small volume. After standing overnight, the crystalline precipitate was collected by suction, washed with little acetic acid, and dried at 140°C. Yield 398 mg (82%), m.p. 352–354°C decomp. (acetic acid).

b) In the same way, 220 mg (1·0 mmol) raw amino derivative *IV* was boiled with 15 ml acetic acid to give the corresponding yield of *IX*.

c) A mixture of 200 mg (1·0 mmol) N-amino derivative *VIII* and 25 ml acetic acid was refluxed 10 h and treated further in the same way as sub *a*) and *b*). Yield 200 mg (83%), m.p. 352 to 354°C decomp. (acetic acid). For $C_{12}H_{10}N_4O_2$ (242·2) calculated: 59·50% C, 4·16% H, 23·13% N; found: 59·44% C, 4·05% H, 23·10% N. IR spectrum (KBr, cm^{-1}): 1 702, 1 723 (ν(C=O)).

1-Benzylideneamino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*X*)

A hot solution of 100 mg (0·5 mmol) N-amino derivative *VIII* in 10 ml acetic acid and 5 ml water was treated with 0·1 ml benzaldehyde, shortly boiled, diluted with about 5 ml water, and cooled. The crystalline precipitate was collected by suction and washed with little ethanol. Yield 140 mg (97%), m.p. 334–336°C. For $C_{17}H_{12}N_4O$ (288·3) calculated: 70·82% C, 4·20% H, 19·44% N; found: 70·56% C, 4·18% H, 19·57% N.

1-(4-Nitrobenzylideneamino)-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*XI*)

The preparation was analogous to the previous one, 100 mg (0·5 mmol) compound *VIII* and solution of 80 mg *p*-nitrobenzaldehyde in 6 ml acetic acid being used. Yield 166 mg (99·8%), m.p. above 360°C. For $C_{17}H_{11}N_5O_3$ (333·3) calculated: 61·26% C, 3·33% H, 21·01% N; found: 61·06% C, 3·26% H, 21·25% N.

1-(4-Chlorobenzylideneamino)-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one (*XII*)

The preparation was analogous to the previous one, 100 mg (0·5 mmol) *VIII* and 75 mg 4-chlorobenzaldehyde being used. Yield 160 mg (99%), m.p. above 360°C. For $C_{17}H_{11}ClN_4O$ (322·8) calculated: 63·26% C, 3·44% H, 17·36% N; found: 63·24% C, 3·45% H, 17·49% N.

1,2-Dihydroimidazo[4,5-*b*]quinolin-2-one (*XIII*)

A mixture of 200 mg (1·0 mmol) N-amino derivative *VIII*, 20 ml water, and 1·5 ml 37% HCl was heated until dissolution and then cooled to 0—3°C. A solution of 70 mg (1·0 mmol) $NaNO_2$ in about 3 ml ice water was added thereto. The mixture was left to stand in ice bath 1 h, heated to room temperature, left to stand overnight, and neutralized by addition of $NaHCO_3$. The crystalline precipitate was collected by suction, washed with water, and dried at 140°C. Yield 180 mg (97%). After recrystallization from acetic acid the decomposition point is 350—354°C, ref.[12] gives m.p. 348—350°C.

The authors are indebted to Mrs H. Špilháčková for carrying out the elemental analyses.

REFERENCES

1. Slouka J., Bekárek V.: J. Prakt. Chem. *316*, 943 (1974).
2. Slouka J.: This Journal *42*, 894 (1977).
3. Tomchin A. B., Ioffe I. S.: Zh. Org. Khim. *8*, 1287 (1972).
4. Ioffe I. S., Tomchin A. B.: Zh. Obshch. Khim. *40*, 859 (1970).
5. Slouka J.: This Journal *44*, 2348 (1979).
6. Hejsek M., Slouka J.: Pharmazie *39*, 186 (1984).
7. Hajpál I., Berényi E.: J. Heterocycl. Chem. *19*, 313 (1982).
8. Hajpál I., Berényi E.: J. Heterocycl. Chem. *19*, 308 (1982).
9. Slouka J., Nálepa K.: J. Prakt. Chem. (4), *18*, 188 (1962).
10. Johnson J. R., Hasbrouck R. B., Durcher J. D., Bruce W. F.: J. Amer. Chem. Soc. *67*, 423 (1945).
11. Reissert A.: Ber. Deutsch. Chem. Ges. *30*, 1030 (1897).
12. Kozák J., Musial L.: Bull. Intern. Acad. Polon. 1930A, 432; Chem. Abstr. *25*, 5400 (1931).
13. Martin G. J., Martin M. L., Gouesnard J. P. in the book: NMR *Basic Principles and Progress* (P. Diehl, E. Fluck, R. Kosfeld, Eds), Vol. 18. Springer, Berlin 1981.

Translated by J. Panchartek.