INDOLE DERIVATIVES

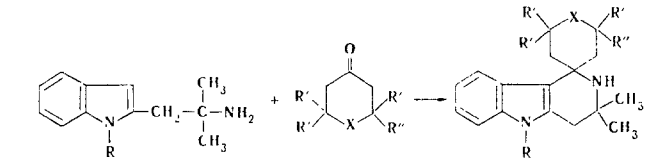
XLI.* CYCLIZATION OF 1-R-2-(β-AMINOISOBUTYL)INDOLES WITH CYCLIC KETONES

N. N. Novikova, I. D. Silenko,
N. F. Kucherova, and V. A. Zagorevskii

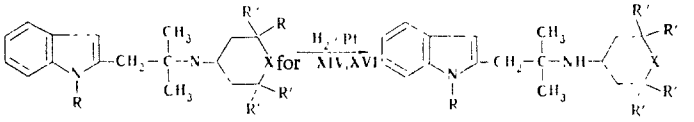
UDC 547.759.3:543.422.25

The cyclization of 1-R-2-(β-aminoisobutyl)indoles with various cyclic ketones forms imines or spiro compounds of the 1,2,3,4-tetrahydro-γ-carboline series, depending on the conditions and the structure of the ketone.

It has been shown previously [2] that the cyclodehydration of 2-(β-aminoethyl)indole and of 2-(β-aminoisobutyl)indole (I) with aldehydes or ketones forms alkyltetrahydro-γ-carbolines. We have continued these investigations and have studied the cyclization of (I) and of 2-(β-aminoisobutyl)-1-methylindole (II) with a number of alicyclic and heterocyclic ketones (III-VIII) in order to obtain previously unknown spiro compounds of the 1,2,3,4-tetrahydro-γ-carboline series. Cyclization was performed in a mixture of absolute ethanol and benzene containing hydrogen chloride. In the condensation of (I) with (III) and (IV) in the presence of catalytic amounts of hydrogen chloride, a single substance was obtained in each case. The PMR spectra of these compounds lacked the signal of the vinyl proton in position 3 of the indole ring in the ~6 ppm region, and on this basis these compounds may be ascribed the structures of 2,2-dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spirocyclohexane (IX) and 2,2-dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-tetrahydrothiopyrone (X), respectively.



I-II III-VIII IX-XIII



XIV-XIX XX, XXI

I R=H, II R=CH$_3$; III R′=R″=H, X=CH$_2$, IV R′=R″=H, X=S, V R′=R″=H X=NCH$_3$, VI R′=CH$_3$, R″=H, X=NH, VII R′=R″=CH$_3$, X=NH VIII R′=R″=CH$_3$, X=NCH$_3$; IX R=R′=R″=H, X=CH$_2$, X=R=R′=R″=H, X=S; XI R=R′=R″=H X=NCH$_3$, XII R=CH$_3$, R′=R″=H, X=CH$_2$, XIII R=CH$_3$, R=R″=H, X=S, XIV R=R′=R″=H, X=NCH$_3$, XV R=R″=H, R′=CH$_3$; X=NH, XVI R=H, R′=R″=CH$_3$, X=NH, XVII R=R′=CH$_3$, R″=H, X=NH, XVIII R=R′=R″=CH$_3$, X=NH; XIX R=R′=R″=CH$_3$, X=NCH$_3$, XX R′=R″=H, X=NCH$_3$, XXI R′=R″=CH$_3$, X=NH

The cyclization of (II) with (III) and with (IV) under conditions analogous to those given above led to the spiro compounds (XII) and (XIII), respectively. As a result of the cyclization of (I) with (V) in a weakly acid medium with the azeotropic distillation of water for 16 h, 2,2-dimethyl-1,2,3,4-tetrahydro-γ-carbo-

* For communication XL, see [1].

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp 942-944, July, 1973. Original article submitted July 14, 1972.

line-4-spiro-4'-(1'-methylpiperidine) (XI) was formed. However, when the same components were boiled in a 29% ethanolic solution of hydrogen chloride for 2 h 30 min, only 4-[1,1-dimethyl-2-(indol-2-yl)ethylimino]-1-methylpiperidine (XIV) was formed. The reaction of (VI, VII, and X) with (I) and with (II) under various conditions formed only the imines (XV-XIX), respectively. In contrast to the spiro compounds, the PMR spectra of the imines (XIV-XIX) each had a signal in the 5.23-5.57-ppm region of the proton of a 3H-indole ring. The imines (XIV and XVI) were reduced catalytically to the corresponding amines (XX, XXI). It is interesting to note that the imine (XIV) is not cyclized into the corresponding spiro compound (XI) under the conditions of the formation of (XI) from (I) and (V). The cyclization of (IV) and also of (XV-XIX) could not be performed under different conditions [for example, the addition of certain amounts of water or of the ketone (V), a change in the concentration of hydrogen chloride, a different solvent]. It follows from this that formation of spiro compounds from (I) and (V) apparently takes place not through the imine (XIV) (or its amino form) but through the hydroxyalkylation by the ketone of the indole compound (I) at position 3 with the subsequent cyclodehydration of the intermediate compound.

EXPERIMENTAL

The PMR spectra were taken on a Varian T-60 spectrometer with HMDS as internal standard.

2-(β-Aminoisobutyl)-1-methylindole (II). With stirring, a solution of 10 g (53 mmoles) of (I) in 60 ml of dimethylformamide was gradually added to a suspension of 1.8 g (75 mmoles) of sodium hydride in 60 ml of dimethylformamide. After 1 h, 6.7 g of methyl iodide was added dropwise at a bath temperature of 50°C, and the mixture was stirred for another 1 h at this temperature and was then poured into water and extracted with ether, and the extract was dried with magnesium sulfate. The addition of an ethereal solution of hydrogen chloride precipitated a hydrochloride, which was filtered off and recrystallized from absolute ethanol. This gave 6.5 g (61%) of (II), mp 167-168°C. Found, %: C 65.3; H 8.0; Cl 14.7; N 11.8. $C_{13}H_{18}N_2 \cdot HCl$. Calculated, %: C 65.4; H 8.0; Cl 14.8; N 11.7.

2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spirocyclohexane (IX). To 2 g (9 mmoles) of the hydrochloride (I) in 10 ml of absolute ethanol were added 1.06 g (0.01 mole) of (III) in 30 ml of absolute benzene and 1 ml of a 22% solution of hydrogen chloride in ethanol, and the mixture was boiled for 18 h, poured into water, and made alkaline with aqueous ammonia. The precipitate that deposited was filtered off, giving 1.5 g of (IX).

2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-tetrahydrothiopyran (X). Similarly, 1.1 g (4.9 mmoles) of the hydrochloride of (I) in 7 ml of absolute ethanol and 0.6 g (51 mmoles) of (IV) in 30 ml of absolute benzene and 1 ml of a 22% solution of hydrogen chloride in ethanol gave 0.9 g of (X).

2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-(1'-methylpiperidine) (XI). To 4 g (18 mmoles) of the hydrochloride of (I) and 3 g (20 mmoles) of the hydrochloride of (V) in 20 ml of absolute ethanol were added 60 ml of absolute benzene and 2 ml of a 30% solution of hydrogen chloride in ethanol. The reaction mixture was boiled for 9 h with the azeotropic distillation of the water. Another 20 ml of absolute ethanol, 60 ml of absolute benzene, and 2 ml of 30% ethanol hydrogen chloride was added, and the benzene and the ethanol were distilled off over 16 h to reduce the reaction mixture to small volume. The hydrochloride that deposited was dissolved in water and the solution was made alkaline with aqueous potassium carbonate, giving 2.8 g of (XI).

2,2,9-Trimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spirocyclohexane (XII). To 0.5 g (2 mmoles) of the hydrochloride (II) in 5 ml of absolute ethanol were added 0.25 g (2.5 mmoles) of (III), 5 ml of a 19% ethanolic solution of hydrogen chloride, and 5 ml of absolute benzene. The reaction mixture was boiled with the azeotropic distillation of water for 3 h 30 min and was left overnight. The precipitate of hydrochloride that deposited was filtered off and was dissolved in water, and the solution was made alkaline with aqueous potassium carbonate, after which 0.3 g of (XII) was isolated in the usual manner.

2,2,9-Trimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-tetrahydrothiopyran (XIII). This was obtained in a similar manner to (XII) from 1 g (4 mmoles) of the hydrochloride of (II) in 10 ml of a 19% ethanolic solution of hydrogen chloride and 0.65 g (5.6 mmoles) of (IV) in 10 ml of absolute ethanol and 10 ml of absolute benzene; yield of (XIII) 0.5 g.

4-[1,1-Dimethyl-2-(indol-2-yl)ethylimino]-1-methylpiperidine (XIV). A mixture of 2 g (9 mmoles) of the hydrochloride of (I), 1.4 g (12 mmoles) of (V) in 10 ml of a 29% solution of hydrogen chloride in ethanol and 10 ml of absolute benzene was boiled with the azeotropic distillation of water for 2 h 30 min.

TABLE 1. Information on Compounds (IX-XIX)

Compound[a]	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IX	156,5—157,5	$C_{18}H_{24}N_2$	80,7	9,0	10,5	80,5	9,0	10,4	63
X	231—232	$C_{17}H_{22}N_2S$[b]			10,0			9,8	64
XI	221—222	$C_{18}H_{25}N_3$	76,5	8,9	14,5	76,3	8,9	14,8	56
XII	153,5—155	$C_{19}H_{25}N_2$	80,6	9,3	9,7	80,8	9,3	9,9	50
XIII	186.5—187,5	$C_{18}H_{24}N_2S$[c]	71,7	8,0	9,5	71,9	8,1	9,3	44
XIV	137—138	$C_{18}H_{25}N_3$	76,4	9.0	14,5	76,3	8,9	14,8	72
XV	108,5—110	$C_{20}H_{29}N_3$	77,4	9,4	13,6	77,1	9,4	13,5	85
XVI	110,5—111.5	$C_{21}H_{31}N_3$	77,2	9,8	13,1	77,5	9,6	12,9	70
XVII	118—119,5	$C_{21}H_{31}N_3$	77,6	9,6	12,9	77,5	9,6	12,9	53
XVIII	144,5—145	$C_{22}H_{33}N_3$	77,8	9,8	12,2	77,8	9,8	12,4	29
XIX	146—147,5	$C_{23}H_{35}N_3$	77,9	10,0	11.7	78,1	10,0	11,9	32

[a]Compounds (IX, XIII, XVI, and XVIII) were recrystallized from a mixture of benzene and petroleum ether, (X) from ethanol, (XI) from benzene, and (XII, XVII, and XIX) from heptane.
[b]Found, %: S 11.1. Calculated, %: S 11.2.
[c]Found, %: S 11.0. Calculated, %: S 10.7.

The hydrochloride that precipitated was filtered off and dissolved in hot water, and the solution was made alkaline with aqueous potassium carbonate. The precipitate was filtered off, giving 1.8 g of (XIV).

4-[1,1-Dimethyl-2-(indol-2-yl)ethylimino]-2,2,6-trimethylpiperidine (XV). A mixture of 2 g (8.8 mmoles) of (I) and 2 g (11 mmoles) of (VI) in 10 ml of a 29% solution of hydrogen chloride in ethanol was boiled for 5 h. The resulting precipitate of the hydrochloride was dissolved in water and the solution was made alkaline with potassium carbonate solution, giving 2.3 g of (XV). Under the conditions for the preparation of (XI), also, only (XV) was formed.

4-[1,1-Dimethyl-2-(indol-2-yl)ethylimino]-2,2,6,6-tetramethylpiperidine (XVI). A mixture of 3.4 g (15 mmoles) of the hydrochloride (I) and 3.4 g (20 mmoles) of (VII) in 20 ml of a 29% solution of hydrogen chloride in ethanol was boiled for 3 h 30 min. In the usual way, 3.4 g (XVI) was obtained. Again only (XVI) was formed under the conditions for the preparation of (XI).

4-[1,1-Dimethyl-2-(indol-2-yl)ethylimino]-1,2,2,6,6-pentamethylpiperidine (XIX). A mixture of 1.5 g (6 mmoles) of the hydrochloride of (II) and 1.2 g of (VIII) in 15 ml of a 30% solution of hydrogen chloride in ethanol was boiled for 3 h and poured into water, and the mixture was made alkaline with an aqueous solution of potassium carbonate and was extracted with ether. The extract was dried with magnesium sulfate and the ether was distilled off. The residue was crystallized from petroleum ether, giving 0.7 g (XIX).

The imines (XVII) and (XVIII) were obtained similarly by the reaction of (II) with (VI) and with (VII), respectively.

Information on substances (IX-XIX) is given in Table 1.

4-[1,1-Dimethyl-2-(indol-2-yl)ethylamino]-1-methyl-4-piperidine (XX). A solution of 0.7 g of (XIV) in 15 ml of methanol was acidified with a solution of hydrogen chloride in ethanol and was hydrogenated under the usual conditions over 50 mg of platinum until the absorption of hydrogen ceased. The catalyst was separated off and the ethanol was distilled off in vacuum. The residue was dissolved in water and the solution was made alkaline with aqueous ammonia and was extracted with ether. The extract was dried with magnesium sulfate, the ether was distilled off, and petroleum ether was added to the residue. The resulting precipitate was filtered off and was twice crystallized from heptane, giving 0.1 g (14%) of (XX), mp 138-139°C. The substance gave a depression of the melting point in admixture with (XIV). Found, %: C 76.0; H 9.7; N 14.5. $C_{18}H_{27}N_3$. Calculated, %: C 75.7; H 9.5; N 14.7. Compounds (XX) and (XIV) differed in their mobility in TLC on Al_2O_3 (activity grade IV, ether).

4-[1,1-Dimethyl-2-(indol-2-yl)ethylamino]-2,2,6,6-tetramethylpiperidine (XXI). As in the preceding case, 2 g of (XVI) was hydrogenated over 0.2 g of Pt, giving (XXI), which was crystallized twice from benzene. Yield 0.15 g, mp 182.5-184°C. The substance gave a depression of the melting point in admixture with (XVI). C 77.2; H 10.1; N 12.8. $C_{21}H_{33}N_3$. Calculated, %: C 77.0; H 10.1; N 12.8.

LITERATURE CITED

1. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 1081 (1972).
2. N. N. Komzolova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 668 (1968).