SYNTHESIS OF 2,3,4,5-TETRAHYDRO-1,5-BENZOX(AND THI)AZEPINES AND THEIR UTILIZATION FOR THE PREPARATION OF CONDENSED INDOLES

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A preparative method is proposed for the synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepine by reductive ring expansion of 4-chromanone and 4-thiochromanone oximes. These compounds were converted to the corresponding N-amino derivatives, which, like arylhydrazines in the Fischer reaction, give new condensed indole systems. The reduction of the oxime (and its tosylate) of 5-oxo-2,3,4,5-tetrahydro-1-benzoxepine was investigated.

Arenoheterocyclenes of the 2,3,4,5-tetrahydro-1,5-benzoxazepine type are relatively difficult-to-obtain and little-investigated compounds.

2,3,4,5-Tetrahydro-1,5-benzoxazepine (I) and 2,3,4,5-tetrahydro-1,5-benzothiazepine (II) are obtained in low yields by reaction of o-aminophenol and 2-mercaptoaniline with 1,3-dihalopropanes [1, 2] or by reduction of chromanone and thiochromanone oximes with lithium aluminum hydride [3, 4]. The well-known method for the synthesis of I, which is based on the reduction of 2,3,4,5-tetrahydro-1,5-benzoxazepin-4-one with lithium aluminum hydride, is limited by the fact that the starting lactam [3, 5, 6] is difficult to obtain.

In the present research we investigated the reduction of 4-chromanone and 4-thiochromanone oximes with $LiAlH_4-AlCl_3$ (1:4) taking into account the fact that the application of the indicated reagent for the reduction of other oximes of aliphatic aromatic ketones raised the yields of products of reductive rearrangement considerably [7, 8]. In fact, it was found that the rearrangement occurred practically completely [only traces of primary amines are detected by thin-layer chromatography (TLC)]. This method for the synthesis of I and II can undoubtedly be extended to various substituted oximes of 4-chromanone and its analogs that are capable of reductive rearrangement (for example, see [9, 10]). Inasmuch as the mechanism of the reductive rearrangement has not been ascertained definitively [4], the accumulation of experimental data, particularly on the effect of substituents in the aromatic portion of the ketoxime and the ring size of the oximine fragment of the molecule on the relative yields of the products of competitive reactions – normal and anomalous reduction – is desirable. It has been noted [3, 8] that 1-indanone oxime is less inclined to undergo rearrangement under the influence of $LiAlH_4$ than 1-tetralone oxime, whereas 1-benzosuberone oxime differs little in this respect from its six-membered homolog [8]. However, it is known [3, 9] that the transition from 4-thiochromanone to 5-homothiochromanone is accompanied by a sharp decrease in the relative rate of the anomalous reaction:* the yields of primary and secondary amines are 27 and 43%, respectively, in the first case, as compared with 74 and 0% in the second case. The effect of the ring size of the corresponding oxygen analogs has not been studied: data on the redution of 5-oxo-2,3,4,5-tetrahydro-1-benzoxepine (III) were not available. We filled this gap. It was ascertained that oxime III reacts with

*We satisfied ourselves that the use of 1 mole of $LiAlH_4$ rather than 3 moles does not change the ratio of the reaction products.

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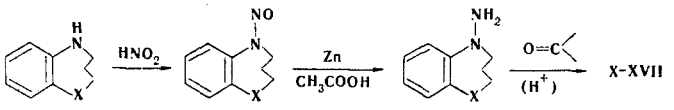
$LiAlH_4$ to give a mixture of a secondary amine – 2H-3,4,5,6-tetrahydro-1,6-benzoxazocine – and 5-amino-2,3,4,5-tetrahydro-%-benzoxepine (V) in relative yields of 34 and 66%, respectively. Consequently, oxime III is more inclined to undergo reductive rearrangement than its sulfur analog, but in this case the oxime of the seven-membered ketone is converted to a ring-expansion product in lower relative yield, inasmuch as the secondary and primary amines are formed in a ratio of 63 and 27% in the reduction of 4-chromanone oximes [3]. The use of a mixture of $LiAlH_4$ and $AlCl_3$ for the reduction of oxime III changes the direction of the reaction in favor of the secondary amine (94% amine IV and 6% amine V). It has been found [4] that it is better to use oxime tosylates to obtained secondary amines. This method proved to be successful in the case of the oxime of III: the relative yields of amines IV and V were 97 and 3%, respectively. Secondary amine IV is formed entirely free of the primary amine by reduction of the tosylate of oxime III with $LiAlH_4-AlCl_3$. Pure IV was isolated in 43% yield in a preparative experiment. It might have been concluded that in the series of oximes of oxygen and sulfur benzoheterocyclenes the latter differ by their lower relative ease of rearrangement. With allowance for the proposed mechanism of the reduction of oximes of similar ketones [4], this difference is apparently determined by the greater electron-donor capacity of the alkoxy group as compared with the thioether group (for example, see [11]). On the other hand, a decrease in the tendency to undergo rearrangement is observed on passing from the six-membered alicycle to the seven-membered alicycle (however, the products of the rearrangement contain seven- and eight-membered rings, respectively), and this is in poor agreement with the relationship discovered for the Beckmann rearrangement of 1-benzocyclene oximes. In addition, it is also probably necessary to take into account the high degree of folding of the sulfur-containing saturated heterocycles and the associated conformational peculiarities [13]. We used I and II, which have become quite accessible, for the synthesis of hydrazines and condensed indoles from them. 2,3,4,5-Tetrahydro-5-amino-1,5-benzoxazepine (VI) and its analog – a hydrazine with a benzothiazepine structure (VII) – were obtained by nitrosation of I and II and reduction of the nitroso derivatives (VIII, IX).



I, II VIII, IX VI, VII

I, VI, VIII X = O; II, VII, IX X = S

Methyl ethyl ketone, cyclohexanone, tetrahydro-4-thiopyrone, 4-piperidone, and 1-methyl-4-piperidone served as the ketone components in the Fischer reaction. The cyclization was carried out by refluxing solutions of the components in absolute alcohol (with the hydrazine in the form of the hydrochloride), without the addition of acid, in the presence of hydrogen chloride or ethylsulfuric acid. As a result, we obtained new polycondensed indole systems (X-XVII, see Table 1). The synthesis of condensed indoles on the basis of hydrazines of the 1-aminoindoline type was previously proposed in [14].

EXPERIMENTAL

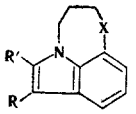
The UV spectra of alcohol solutions of the compounds ($c = 10^{-4}-10^{-3}$ M) were recorded with an SF-4 spectrophotometer. The IR spectra were obtained with a UR-10 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer on the δ scale.

The purity of the compounds obtained was monitored by means of thin-layer chromatography (TLC) on Al_2O_3 (alkaline form); in the reduction of the oximes, the starting ketones, ketoximes, and the resulting amines were identified by comparison with authentic substances.

2,3,4,5-Tetrahydro-1,5-benzoxazepine (I). A 32.5-g (0.24 mole) sample of anhydrous $AlCl_3$ and a suspension of 2.33 g (0.061 mole) of $LiAlH_4$ in 80 ml of ether were added successively in small portions with cooling to 200 ml of absolute ether, after which the mixture was stirred for 1.5 h. A solution of 10 g (0.061 mole) of 4-chromanone oxime in 100 ml of ether was added, and the mixture was refluxed for 9 h. It was then decomposed, initially with moist ether and then with water until the resulting solid dissolved. The aqueous solution was separated, washed with ether (the ether extract contained the neutral product and a small amount of the starting oxime), made alkaline with 10% potassium hydroxide solution, and extracted with ether. The extract was dried with magnesium sulfate and evaporated to give 5.5 g (60.2%) of I (containing traces of primary amine) with mp 51-53° (from petroleum ether) (mp 53-54° [4]) and R_f 0.73 (activity IV Al_2O_3, chloroform). According to [4], authentic 4-aminochroman has R_f 0.26.

2,3,4,5-Tetrahydro-1,5-benzothiazepine (II) Hydrochloride. This compound was similarly obtained from 0.15 mole of 4-thiochromanone oxime, 0.15 mole of $LiAlH_4$, and 0.6 mole of $AlCl_3$ with subsequent

TABLE 1. Condensed Indoles (X-XVII)



Compound	X	R+R'	Synthetic meth	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	S	C	H	N	S	
X	O[a]		B	78—79 (from hexane)	$C_{13}H_{15}NO$[b]	77,7	7,9	7,0		77,6	7,5	6,9		60
XI	O	$(CH_2)_4$	B	88—89 (from absolute alcohol)	$C_{15}H_{17}NO$	79,4	7,6	6,3		79,3	7,5	6,2		65
XII	S	$(CH_2)_4$	A	104—105,5 (from heptane)	$C_{15}H_{17}NS$	74,3	7,2	5,8	13,4	74,0	7,0	5,8	13,2	66
XIII	S	$CH_2N(CH_3)CH_2CH_2$	A	84—85 (from heptane – benzene)	$C_{15}H_{18}N_2S$[c]	69,7	6,9	10,8	13,0	69,5	7,0	10,8	12,4	39
XIV	O	$CH_2N(CH_3)CH_2CH_2$	A	250—251 (from water)	$C_{15}H_{18}N_2O$[d]· ·HCl	64,2	6,8	10,0		64,4	6,9	10,0		58
XV	S	$CH_2SCH_2CH_2$	C	145—145,5 (from benzene)	$C_{14}H_{15}NS_2$[e]	64,3	5,8	5,3	24,5	64,3	5,8	5,3	24,5	82
XVI	O	$CH_2SCH_2CH_2$	B	143—144	$C_{14}H_{15}NOS$	68,4	6,2	6,0	12,7	68,6	6,2	5,7	13,0	58
XVII	S	$CH_2NHCH_2CH_2$	C	278 (dec., from aqueous alcohol)	$C_{14}H_{16}N_2S$[f]· ·HCl	59,5	6,0	10,1	11,8	59,8	6,1	10,0	11,4	56

[a] R = R' = CH_3. [b] IR spectrum (in mineral oil), cm^{-1}: 1615, 1590, and 1570. [c] UV spectrum, λ_{max} (log ε), nm: 232 (4.42), 258 (4.1), and 300 (3.9); IR spectrum (in mineral oil), cm^{-1}: 1610 and 1580. [d] Found: Cl 12.4%. Calculated: Cl 12.7%. [e] IR spectrum (in mineral oil), cm^{-1}: 1600 and 1570. [f] Found: Cl 12.6%. Calculated: Cl 12.6%.

treatment of base II with a solution of hydrogen chloride in ether. The yield of product with mp 202-204° (from isopropyl alcohol) (mp 205.5-207° [3]) was 17.2 g (80.5%).

5-Oxo-2,3,4,5-tetrahydro-1-benzoxepine Oxime Tosylate (III). A mixture of 0.85 g (5 mmole) of oxime III and 1.04 g (5.5 mmole) of p-toluenesulfonyl chloride in 4 ml of pyridine was allowed to stand for 5 h, after which it was poured into 20 ml of water and 6 ml of concentrated HCl. The acid mixture was allowed to stand in a refrigerator for ~16 h, and the resulting crystals were removed by filtration and washed with water and petroleum ether to give 1.3 g (82%) of the tosylate with mp 88.5° (dec., from absolute alcohol). Found: C 62.1; H 5.1; N 4.3; S 9.6%. $C_{17}H_{17}NO_4S$. Calculated: C 61.6; H 5.2; N 4.2; S 9.7%.

2H-3,4,5,6-Tetrahydro-1,6-benzoxazocine (IV) Hydrochloride. A 3.31-g (0.01 mole) sample of oxime tosylate III was added in portions to a prepared solution (0.04 mole of $AlCl_3$ and 0.01 mole of $LiAlH_4$) in 160 ml of ether, and the resulting mixture was refluxed for 9 h. It was then decomposed with 20 ml of moist ether, 20 ml of water, and 40 ml of 20% sodium hydroxide solution and extracted with ether. The ether solutions were extracted with 10% HCl solution, and the aqueous solutions were vacuum evaporated to dryness. The residue was crystallized from absolute alcohol – ether to give 0.186 g (43%) of the hydrochloride of IV with mp 240° (dec.) and R_f 0.9 [activity VI Al_2O_3, benzene – chloroform (10 : 1)]. Found: C 60.3; H 7.1; Cl 17.7; N 7.2%. $C_{10}H_{13}NO \cdot HCl$. Calculated: C 60.1; H 7.1; Cl 17.7; N 7.0%. PMR spectrum of base IV (in CCl_4): 1.62 (m, 4H, CCH_2CH_2C) 3.50 (m, 3H, NH, and NCH_2), 4.05 (m, 2H, OCH_2), and 6.55 ppm (m, 4H, C_6H_4). For proof of the structure of amine IV, ketone III was converted by the Schmidt reaction [15] to 2H-3,4,5,6-tetrahydro-1,6-benzoxazocin-5-one (which we also obtained by Beckmann rearrangement of oxime III) and reduced with $LiAlH_4$ to IV [15], which was characterized in the form of the hydrochloride.

5-Amino-2,3,4,5-tetrahydro-1-benzoxepine (V). A solution of 2.66 g (0.15 mole) of oxime III in 200 ml of ether was added to 0.57 g (0.015 mole) of $LiAlH_4$ in 25 ml of ether, and the mixture was refluxed for 9 h. It was then decomposed with 20 ml of moist ether, 20 ml of water, and 20 ml of 20% sodium hydroxide solution and extracted with ether. The ether extracts were extracted with 10% HCl solution, and the hydrochloric acid solutions were vacuum evaporated. The residue (a mixture of the hydrochlorides of IV and V)

was dissolved in 10 ml of water, and the resulting solution (solution A) was filtered. The filtrate was made alkaline to pH 2 with saturated $NaHCO_3$ solution, 5 ml of acetate buffer was added, and the mixture was extracted with ether to give 0.16 g of secondary amine IV. Sodium carbonate was added to pH 8 to the aqueous solution, and the alkaline mixture was extracted successively with ether and ethyl acetate. The combined extracts were evaporated, and the residual oil was dissolved in ether. The hydrochloride was precipitated by the addition of an ether solution of hydrogen chloride and crystallized from absolute alcohol–ether to give 0.8 g (33%) of the hydrochloride of V with mp 260° (dec.) and R_f 0.2. Found: C 60.1; H 7.1; Cl 17.7; N 7.3%. $C_{10}H_{13}NO \cdot HCl$. Calculated: C 60.1; H 7.1; Cl 17.7; N 7.3%. PMR spectrum of base V (in CCl_4): 1.8 (m, 6H, NH_2 and CCH_2CH_2C), 4.05 (m, 3H, 5-H and OCH_2) and 7.05 ppm (m, 4H, C_6H_4). For the determination of the relative yields of amines IV and V, an aliquot of solution A containing the mixture of hydrochlorides was made alkaline, and the bases were extracted and analyzed by PMR spectroscopy in CD_3COOD solutions; the basis of this analysis is the fact that the 5-H signal of V appears separately at 4.8 ppm (monitoring with respect to a genuine sample).

2,3,4,5-Tetrahydro-5-nitroso-1,5-benzothiazepine (IX). A total of 6.35 g (0.0925 mole) of a concentrated solution of sodium nitrite was added gradually at 0° to 12.2 g (0.074 mole) of II in 65 ml of 15% sulfuric acid, and the mixture was stirred for 30 min. The resulting precipitate was separated to give 13.2 g (92%) of nitrosoamine IX with mp 85-87° (from 2-propanol). Found: C 56.1; H 5.2; N 14.4; S 16.6%. $C_9H_{10}N_2OS$. Calculated: C 55.7; H 5.2; N 14.4; S 16.5%.

2,3,4,5-Tetrahydro-5-amino-1,5-benzothiazepine (VII) Hydrochloride. A 31.5-ml sample of glacial acetic acid was added dropwise to a mixture of 12 g (0.062 mole) of IX and 31.5 g (0.75 g-atom) of zinc dust in 140 ml of methanol at 14-16°, after which the mixture was stirred at 14-16° for 3 h and at 20° for 16 h. The solution was separated, vacuum evaporated to 80 ml, made strongly alkaline, and extracted with ether. The ether solution was dried with magnesium sulfate and treated with hydrogen chloride to precipitate 11.6 g (83.7%) of hydrochloride VII with mp 190-191° (from alcohol). Found: C 49.8; H 6.1; Cl 16.3; N 12.9; S 14.7%. $C_9H_{12}N_2S \cdot HCl$. Calculated: C 49.9; H 6.0; Cl 16.4; N 12.9; S 14.8%.

2,3,4,5-Tetrahydro-5-amino-1,5-benzoxazepine (VI) Hydrochloride. The method used to obtain the hydrochloride of VII was used to obtain this compound by nitrosation of I and subsequent reduction of nitroso derivative VIII (without isolation in pure form). The yield of the hydrochloride of VI with mp 172-173.5° (dec., from 2-propanol) was 61%. Found: C 53.9; H 6.6; Cl 17.7; N 14.0%. $C_9H_{12}N_2O \cdot HCl$. Calculated: C 53.9; H 6.6; Cl 17.7; N 14.0%.

Synthesis of Indoles X-XVII. Method A. A mixture of 0.7 g (3 mmole) of the hydrochloride of VII and 0.35 g (3.7 mmole) of cyclohexanone in 10 ml of 15% HCl in absolute alcohol was refluxed for 10 min, after which it was poured into water, and the resulting precipitate was removed by filtration to give 0.52 g of indole XII.

Method B. A 0.5-g (2.4 mmole) sample of the hydrochloride of VI was refluxed for 3 min with 0.28 mmole of cyclohexanone in 5 ml of absolute alcohol. Workup gave 0.37 g of indole XI.

Method C. A 1-g (4.5 mmole) sample of the hydrochloride of VII was refluxed for 1 h with 0.6 g (5 mmole) of tetrahydro-4-thiopyrone with a solution prepared from 0.5 g of concentrated sulfuric acid and 10 ml of absolute alcohol. Workup gave 1 g of indole XV.

The other indole derivatives (Table 1) were obtained by the indicated methods; in the synthesis of XIII, XIV, and XVII the starting piperidones were used in the form of their hydrochlorides, the reaction mixtures were made alkaline with potassium carbonate, and the bases, which were converted to the hydrochlorides in the case of XIV and XVII, were isolated. A 9% solution of hydrogen chloride in alcohol was used in the preparation of indole XIV. In the case of X, the crude product was purified by chromatography with a column filled with activity IV Al_2O_3 and elution with hexane.

LITERATURE CITED

1. G. S. Sidnu, G. Thyagarajan, and V. Bhalrao, Indian J. Chem., 2(5), 211 (1964).
2. L. K. Mushkalo and I. P. Fedorova, Ukr. Khim. Zh., 20, 305 (1954).
3. V. A. Zagorevskii and N. V. Dudykina, Zh. Obshch. Khim., 34, 2284 (1964).
4. V. A. Zagorevskii, N. V. Dudykina, and L. M. Meshcheryakova, Khim. Geterotsikl. Soedin., 302 (1970).
5. D. Huckle, I. M. Lockhart, and M. Wright, J. Chem. Soc., 1137 (1965).
6. V. Bhalrao and G. Thyagarajan, Indian J. Chem., 7, 429 (1969).

7. M. N. Rerick, C. H. Trottier, R. A. Daignault, and J. D. Defoe, Tet. Letters, 10, 629 (1963).
8. I. Humbert and A. Laurend, Compt. Rend., 272, 1165 (1971).
9. N. V. Dudykina and V. A. Zagorevskii, in: Synthesis of Natural Compounds and Their Analogs and Fragments [in Russian], Zh. Obshch. Khim., 134 (1965).
10. N. Inoue, S. Yamaguchi, and S. Ito, Bull. Chem. Soc. Japan, 41, 2078 (1968).
11. C. K. Ingold, Theoretical Foundations of Organic Chemistry [Russian translation], Mir, Moscow (1973), p. 253.
12. R. Huisgen, J. Witte, H. Walz, and W. Jira, Ann., 604, 191 (1957).
13. A. S. Zefirov and I. V. Kazimirchik, Usp. Khim., 43, 252 (1974).
14. A. N. Kost, L. G. Yudin, and S. A. Popravko, Zh. Obshch. Khim., 32, 1544 (1962).
15. D. Misiti, V. Rimatori, and F. Gatta, J. Heterocycl. Chem., 10, 689 (1973).