PREPARATION OF PRIMARY ALIPHATIC AND ALICYCLIC AMINES FROM THIOPHENE DERIVATIVES

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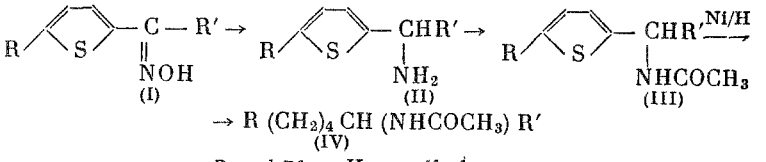
One of us and Ibragimova have shown that N, N-dialkyl-2-thenylamines and 5-(dialkylaminomethyl)-2-thiopheneethanols [1] can be used in the preparation of various aliphatic dialkylamines and amino alcohols by reductive desulfurization. It was of interest to study the possibility of synthesizing primary aliphatic amines in this way, inasmuch as just this sort of base will often form an important fragment in the structure of physiologically active substances. The first attempts in this direction did not give satisfactory results, for treatment of the appropriate thenylamines with Raney nickel gave complex mixtures. The formation of these was probably associated with the fact that ethanol, which was used as reaction medium, has an alkylating effect in presence of this catalyst [2]; moreover, the process may be complicated also by the fact that nickel is capable of bringing about the cleavage of not only the C–S bond, but also the C–N bond (see e.g. [3]).

It will be quite obvious that alkylation of the amino group can be prevented by previous acylation. Such "protection" is useful also in that it stabilizes the carbon-nitrogen bond, at least under the conditions of the reductive desulfurization of thiophene derivatives. We have already shown this to be so in several cases [4]. Our observations led to a method of preparing primary aliphatic amines, which in outline is as follows:

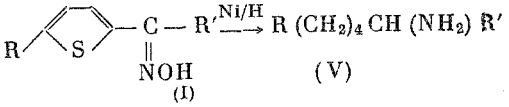


$\rightarrow$ R $(CH_2)_4$ CH $(NHCOCH_3)$ R′
(IV)

R and R′ = H or alkyl.

Both aldoximes and ketoximes may be used here as starting compounds; the reduction is carried out with the aid of amalgamated aluminum, and the desulfurization with the aid of Raney nickel in methanol. In this way we prepared the N-acetyl derivatives of 1-methylpentylamine 6,6-dimethylheptylamine, and pentylamine in yields of 70%, 88%, and 71%, respectively, in the last stage.

Although this method is fairly satisfactory, it would be more convenient to use a method in which it is unnecessary to carry out the reduction to the thiophene amine as a separate operation and which is therefore analogous to the method that we used for the preparation of some amino acids from hydroxyimino acids [5].

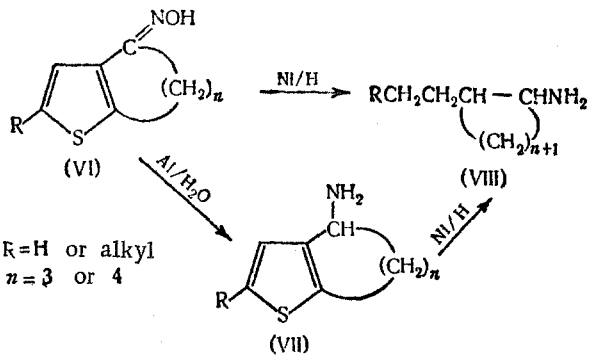


R and R′ = H or alkyl.

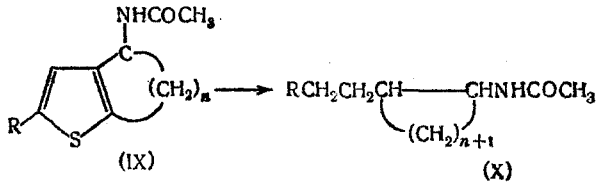
As will be seen from the above, to diminish the possibility of the formation of a mixture of amines it is necessary to ensure that the conditions under which desulfurization is effected with Raney nickel are such that the alkylation of the amino group occurs to the least possible extent. In this matter the observations of Reeve and Christian [6] were found useful; these indicate that in presence of ammonia there is partial suppression of the formation of secondary and tertiary amines. There are also data [7] indicating that when methanol is used no alkylation of amines with

the alcohol occurs, because under these conditions it does not form formaldehyde. Taking these factors into account, we carried out the reductive desulfurization of methyl thienyl ketone oxime and obtained 1-methylpentylamine in 40% yield. However, under the same conditions aldoximes gave the corresponding amines only in very low yields. The cause of this lies in the fact that, as was first shown by Paul [8] and was recently confirmed on the basis of extensive material by Field and co-workers [9], only aldoximes undergo the Beckmann rearrangement in presence of Raney nickel. In an experiment with 2-thiophenecarboxaldehyde oxime we actually detected the formation of valeramide, the product of the reductive desulfurization of 2-thiophenecarboxamide. An analogous phenomenon probably occurs also in the reaction with 5-t-butyl-2-thiophenecarboxaldehyde oxime, but in this case we did not succeed in isolating the pure aliphatic amide. These results prompted us to investigate the action on 2-thiophenecarboxaldehyde oxime of skeletal cobalt, which, as far as we know, is not one of the agents which bring about the Beckmann rearrangement, and which, as a catalyst for the hydrogenation of oximes, gives better yields of primary amines [6]. Under these conditions we isolated pentylamine in 40% yield.

These experiments formed a necessary stage in the study of the more complex and interesting problem of preparing some alicyclic amines whose synthesis by the usual methods is not always possible, namely C-substituted cyclohexyl- and cycloheptylamines. As starting compounds we used the thiophenocycloalkanone oximes that we have described previously [10]. Here it was considered desirable to investigate both possible alternatives for attaining the required object: a) direct desulfurization of these oximes, and b) their reduction to thiophene amines with subsequent hydrogenolysis to alicyclic amines:



As would be expected, the 2-alkylcycloalkylamines were obtained as mixtures of cis and trans isomers. We succeeded in resolving such a mixture only in the case of the isomeric 2-ethylcyclohexylamines, previously described by King and co-workers [11]. This was achieved by acetylating the mixture of amines with acetic anhydride with subsequent treatment of the mixture of acetyl derivatives with hydrochloric acid*, separating the nonhydrolyzing acetyl derivative of the trans isomer, isolating cis-2-ethylcyclohexylamine base from the mother solution, and preparing and crystallizing its picrate. trans-2-Ethylcyclohexylamine was isolated from the picrate obtained directly from the mixture of amines formed in the treatment of 2',3'-thiopheno-1,2-cyclohexan-3-one oxime with Raney nickel. In the case of 2-ethyl- and 2-propylcycloheptylamines, which have not been described in the literature, from the mixture of cis and trans isomers we succeeded in isolating only one of the stereoisomers in the pure state (judging from the constancy of the melting points of the acetyl derivatives). On treatment of 3-acetamido-2',3'-thiopheno-1,2-cyclohexane, 3-acetamido-2',3'-thiopheno-1,2-cycloheptane, and 3-acetamido-5'-methyl-2',3'-thiopheno-1,2-cycloheptane** with Raney nickel, we obtained mixtures of the cis and trans N-acetyl derivatives of 2-ethylcyclohexylamine, 2-ethylcycloheptylamine, and 2-propylcylcloheptylamine, respectively:



R=H or CH_3, $n=3$ or 4.

*Preliminary experiments showed that under these conditions trans-N-acetyl-2-ethylcyclohexylamine is hydrolyzed very slowly.

**According to Patterson [12] this compound should be called 4-acetamido-5,6,7,8-tetrahydro-2-methyl-4H-cycloheptal[b] thiophene.

In the case of the mixture of N-acetyl-2-ethylcyclohexylamines we succeeded in isolating the cis and trans isomers of 2-ethylcyclohexylamine, which were characterized as picrates, m.p. 189° and 198-199° respectively.

EXPERIMENTAL

Preparation of Thiophene Amines by the Reduction of Oximes

2-Thenylamine (II; R and R' = H). A solution of 8.1 g of 2-thiophenecarboxaldehyde oxime (I; R and R' = H) in a mixture of 200 ml of methanol and 50 ml of water was added to amalgamated aluminum prepared from 25 g of aluminum in the form of grains. The mixture was shaken for nine hours; much heat was evolved at the start. Aluminum hydroxide was filtered off and washed several times with methanol. The combined filtrates were acidified with hydrochloric acid and vacuum-evaporated down to about 50 ml. The solution was treated with activated charcoal, and the filtrate was made alkaline with solid potassium hydroxide. The oil that separated was extracted with ether. The extract was dried with potassium hydroxide, and ether was distilled off. By distillation of the residue we isolated 4.4 g (62%) of 2-thenylamine as a colorless liquid; b.p. 75° (16 mm); n_D^{20} 1,5673. The literature [13] gives: b.p. 77° (16 mm); n_D^{15} 1,5678.

After crystallization from dilute alcohol the picrate of this amine had m.p. 179-180°. The literature [14] gives m.p. 181-182°. N-Acetyl-2-thenylamine (III; R and R' = H) was prepared in 72% yield by the action of excess of acetic anhydride on 2-thenylamine; b.p. 145-146° (1.5 mm); 48-50° (from heptane). The literature [15] gives: b.p. 144-152° (1 mm); 44-45°.

The previously undescribed N-(phenylsulfonyl) derivative of 2-thenylamine was prepared as follows. A solution of 1.8 g of benzenesulfonyl chloride in 2 ml of pyridine was added to a solution of 1.0 g of 2-thenylamine in 2 ml of pyridine, and the mixture was heated to boiling, cooled, and poured into 25 ml of water; the mixture was acidified with hydrochloric acid. The oil that separated solidified on cooling. We obtained 1.64 g (94%) of product, m.p. 76.5-77.5° after crystallization from dilute alcohol. Found: C 52.24, 52.35; H 4.50, 4.50; S 25.11, 25.19%. $C_{11}H_{11}O_2NS_2$. Calculated: C 52.15; H 4,38; S 25.32%.

Analogously, by the reduction of the oximes of 5-t-butyl-2-thiophenecarboxaldehyde (I; R = t-C_4H_9, R' = H), methyl thienyl ketone (I; R = H, R' = CH_3), 2',3'-thiopheno-1,2-cyclohexan-3-one (VI; R = H, n = 3), 2',3'-thiopheno-1,2-cycloheptan-3-one (VI; R = H, n = 4), and 5'-methyl-2',3'-thiopheno-1,2-cycloheptan-3-one (VI- R = CH_3, n = 4) we obtained 5-t-butyl-2-thenylamine (II, R = t-C_4H_9, R' = H), α-methyl-2-thenylamine (II; R = H, R' = CH_3), 3-amino-2',3'-thiopheno-1,2-cyclohexane (VII; R = H, n = 3), 3-amino-2',3'-thiopheno-1,2-cycloheptane (VII; R = H, n = 4), and 3-amino-5'-methyl-2',3'-thiopheno-1,2-cycloheptane (VII; R = CH_3, n = 4). For the yields of the amines, their constants, and the constants of suitable derivatives see Table 1. The α-methyl-2-thenylamine obtained contained an appreciable amount of impurity.

Preparation of Thiophene Amines by the Leuckart Reaction

2-Thenylamine (II; R = H, R' = H). 27 g of 2-thiophenecarboxaldehyde was added to 90 g of formamide at 165° over a period of 20 minutes (the formamide was prepared by heating 158 g of ammonium carbonate with 90 ml of 85% formic acid); about 20 ml of turbid liquid was distilled off, and from this, after saturation with ammonium sulfate, we isolated unchanged aldehyde. The latter was returned to the flask containing the reaction mixture. The mixture was heated for five hours with gradual rise in temperature from 165° to 190°. The resulting dark-yellow mass was boiled for two hours with 150 ml of concentrated hydrochloric acid, and the mixture was then diluted with 100 ml of water and saturated with potassium hydroxide. The oil that was liberated was steam-distilled off into a receiver containing 10% hydrochloric acid. The hydrochloric acid solution was evaporated to dryness, the residue was dissolved in water, and the amine was liberated by the addition of alkali and was extracted with ether. The extract was dried over potassium hydroxide, and distillation then gave 17 g (63%) of 2-thenylamine; b.p. 80-85° (17 mm); n_D^{20} 1,5661; d_4^{20} 1,1144.

α-Methyl-2-thenylamine was prepared in 59% yield by the method described previously [18]; b.p. 86.5-87° (17 mm); n_D^{20} 1,5450.

Preparation of Aliphatic and Alicyclic Amines by the Reductive Desulfurization of Oximes with Raney Nickel or Skeletal Cobalt

6.6-Dimethylheptylamine (V; R = t-C_4H_9, R' = H). About 72 g of Raney nickel was added with stirring to a solution of 12.1 g of 5-t-butyl-2-thiophenecarboxaldehyde oxime (I; R = t-C_4H_9, R' = H; m.p. 110°; for its preparation see [4]) in 200 ml of methanol and 60 ml of concentrated ammonia solution at room temperature. The temperature of the mixture rose spontaneously to 44°. The mixture was stirred at 65° for four hours (until the reaction for sulfur with sodium nitroprusside was negative) and then for a further seven hours at the same temperature. Nickel was

filtered off and washed with methanol and water. Solvents were distilled from the combined filtrates under somewhat reduced pressure; the condensate was collected in a receiver containing dilute hydrochloric acid. The residue in the flask was dissolved in chloroform, and the solution was filtered and vacuum-evaporated. We obtained 1.23 g of crystals, which after several crystallizations from hexane had m.p. 156-157° and, judging from its analysis and melting point, was not 6,6-dimethylheptanamide, for which the literature [20] gives m.p. 106°. The structure of the product was not established.

The hydrochloric solution (see above) was vacuum-evaporated, the dry residue was dissolved in water, and the solution was treated with activated charcoal and saturated with potassium hydroxide. The oil was extracted with ether, the extract was dried over potassium hydroxide, and distillation gave 2.7 g (28%) of 6,6-dimethylheptylamine, b.p. 110-115° (70 mm), from which we prepared a picrate, m.p. 171-172°.

Pentylamine (V; R and R' = H). In the hydrogenolysis of 2-thiophenecarboxaldehyde oxime (I; R and R' - H) with Raney nickel under the conditions described above we obtained pentylamine in about 2% yield; after being crystallized from dilute alcohol the picrate had m.p. 135-136.5°. From the reaction mixture we isolated valeramide, m.p. 105-106° (from hexane and dilute alcohol), in 17% yield. The literature [21] gives m.p. 106-106.5°. Found: N 13.87, 14.16%. $C_5H_{11}NO$. Calculated: N 13.82%.

Pentylamine (V; R and R' = H). 70 g of skeletal cobalt was added to a solution of 7.0 g of 2-thiophenecarboxaldehyde oxime (I; R and R' = H) in 100 ml of methanol and 40 ml of 25% ammonia solution at 50°. The mixture was stirred for four hours at 65-70°. As a sample of the solution gave a positive reaction for sulfur, a further 30 g of skeletal cobalt was added, and the mixture was heated until the reaction for sulfur was negative (a further ten hours). Cobalt was filtered off and washed with methanol. The filtrates were combined, acidified with hydrochloric acid, and vacuum-evaporated. The dry residue was dissolved in 40 ml of water, and the solution was decolorized with activated charcoal and saturated with potassium hydroxide. The oil that was liberated was extracted with ether, the extract was dried with potassium hydroxide, and ether was distilled off into a receiver containing dilute hydrochloric acid. Distillation of the residue remaining after the removal of ether gave 0.58 g of pentylamine, b.p. 94-96° and n_D^{20} 1.4105; the picrate had m.p. 137-138° and its analysis was in good accord with the calculated figures (Table 2). After the evaporation of the hydrochloric solution there remainted 1.8 g of pentylamine hydrochloride, from which we prepared a picrate of m.p. 135.5-136.5°. The literature [22] gives: b.p. 104-104.1°, n_D^{20} 1.4104; picrate, m.p. 139.5-140°. In this experiment we did not succeed in isolating any valeramide.

1-Methylpentylamine (II; R = H, R' = CH_3). About 70 g of Raney nickel was added to a solution of 12.0 g of methyl thienyl ketone (I; R = H, R' = CH_3; m.p. 113-114°) in 200 ml of methanol and 60 ml of concentrated ammonia solution at 45° (there was a spontaneous rise of temperature). Stirring was continued for nine hours at 65°. Nickel was filtered off and washed with methanol. From the combined filtrates acidified with hydrochloric acid by the method given above we isolated 3.45 g (40%) of 1-methylpentylamine, whose properties, together with the properties of its picrate and benzoyl derivative, are given in Table 2.

trans-2-Ethylcyclohexylamine (VIII; R = H, n = 3). By the hydrogenolysis of 25 g of 2',3'-thiopheno-1,2-cyclohexan-3-one oxime (VI; R = H, n = 3) with the aid of 140 g of Raney nickel by the method given for 1-methylpentylamine we obtained 9.51 g (50%) of a mixture of cis- and trans-2-ethylcyclohexylamines, from which we prepared a mixture of the picrates, m.p. 193-196°, and a mixture of the phenylsulfonyl derivatives, m.p. 113-119°. For the phenylsulfonyl derivative the literature [11] gives: cis isomer, m.p. 161°; trans isomer, m.p. 131°. Analysis of these mixtures of derivatives gave good agreement between found and calculated values (see Table 2). By crystallization of the mixture of picrates we obtained trans-2-ethylcyclohexylamine picrate, m.p. 198-199°. The literature [11] gives m.p. 198-199°.

2-Ethylcycloheptylamine (VIII; R = H, n = 4). By the hydrogenolysis of 8.0 g of 2',3'-thiopheno-1,2-cycloheptan-3-one (VI; R = H, n = 4) with the aid of 60 g of Raney nickel by the method given above we obtained 3.9 g of a mixture of cis- and trans-2-ethylcycloheptylamines, the properties of which are given in Table 2. By the action of picric acid on the mixture of isomeric amines we prepared a mixture of picrates of m.p. 157-165°, by the crystallization of which from dilute methanol we isolated an isomer of m.p. 177-178°. For the analysis of the mixture of picrates and of one of the isomers see Table 2. By the action of benzenesulfonyl chloride on the mixture of isomeric amines we obtained a 68% yield of a mixture of phenylsulfonyl derivatives, by the crystallization of which from dilute alcohol we isolated the isomer of m.p. 107-108° (see Table 2).

Preparation of trans-2-Ethylcyclohexylamine by the Reductive Desulfurization of 3-Amino-2',3'-thiopheno-1,2-cyclohexane

trans-2-Ethylcyclohexylamine (VIII; R = H, n = 3) was dissolved in 400 ml of methanol, and about 66 g of Raney nickel was added to this solution. Stirring at 60-62° continued for seven hours. Nickel was filtered off and washed with methanol. The combined filtrates were acidified with hydrochloric acid and vacuum-evaporated. The residue was dissolved in water, and the solution was decolorized with charcoal and made alkaline with potassium hydroxide. The oil was extracted with ether, and the extract was dried with potassium hydroxide. By distillation of the extract we isolated 2.7 g of a mixture of amines (yield about 30%); b.p. 61-66° (16 mm); n_D^{20} 1,4582. From the mixture of amines we prepared a mixture of picrates, m.p. 140-175°, by the crystallization of which from dilute alcohol we isolated trans-2-ethylcyclohexylamine picrate, m.p. 198-199°. By the action of 40% potassium hydroxide solution on 8.2 g of the picrate of m.p. 198-199° and subsequent ether extraction and distillation we obtained 2.2 g (75%) of the amine, b.p. 171-172° (746 mm) and n_D^{21} 1,4525, from which we again prepared the picrate of m.p. 197-198°. By treatment of the amine isolated from the picrate with acetic anhydride we obtained trans-N-acetyl-2-ethylcyclohexylamine in 75% yield; m.p. 125.5-126° after crystallization from dilute alcohol.

Preparation of N-Acetyl Derivatives of Aliphatic Amines by the Reductive Desulfurization of N-Acetyl Derivatives of Thiophene Amines

N-Acetylpentylamine (IV; R = H, R' - CH_3). About 60 g of Raney nickel was added to a solution of 9.58 g of N-acetyl-2-thenylamine (III; R = H, R' = CH_3) in 150 ml of alcohol. The mixture was stirred at 65-70° for 11 hr (after this the solution gave a negative reaction for sulfur). Nickel was filtered off and washed with alcohol and water, and the filtrates were combined and vacuum-evaporated. The gel-like residue was dissolved in 60 ml of chloroform, the solution was filtered, and solvent was vacuum-distilled off. Distillation of the residue gave 5.74 g (71%) of N-acetylpentylamine; b.p. 110-112° (2 mm); n_D^{20} 1,4441. From 4.7 g of N-acetylpentylamine, by heating with 5 ml of 3 N HCl and evaporation of the solution, we obtained 4.05 g (90%) of unpurified pentylamine hydrochloride, m.p. 218-228° (decomp.). From this hydrochloride we prepared a picrate in 60% yield; after being crystallized from dilute alcohol it had m.p. 139-140°, undepressed by admixture of pentylamine picrate prepared in another way (see above).

N-Acetyl-6,6-dimethylheptylamine (IV; R = t-C_4H_9, R' = H). About 70 g of Raney nickel was added to a solution of 11 g of N-acetyl-5-5-butyl-2-thenylamine (III; R = t-C_4H_9, R' = H) in 150 ml of methanol at 50°. The mixture was stirred for 11 hours at 65-70° (the solution gave a negative reaction for sulfur after five hours). Nickel was filtered off and washed with methanol. Solvent was distilled off, and vacuum distillation of the residue gave 8.5 g of N-acetyl-6,6-dimethylheptylamine the properties and analysis of which are given in Table 2. 3.86 g of N-acetyl-6,6-dimethylheptylamine was boiled for six hours with 40 ml of 3 N HCl, after which hydrochloric acid was vacuum-distilled off and the residue was dried over phosphoric anhydride. We obtained 3.64 g (98%) of 6,6-dimethylheptylamine hydrochloride as a thick oil, which crystallized out on long standing. From 0.52 g of the hydrochloride by the addition of saturated aqueous picric acid we obtained 1 g (92%) of 6,6-dimethylheptylamine picrate, which was recrystallized from 50% alcohol. The properties and analysis of this picrate are given in Table 2.

N-Acetyl-1-methylpentylamine (IV; R = H, R' = CH_3). About 50 g of Raney nickel was added to a solution of 8.6 g of N-acetyl-α-methyl-2-thenylamine (III; R = H, R' = CH_3) in 150 ml of alcohol at 50-55°. The mixture was stirred at 65-70° for 13 hr, and nickel was then filtered off and washed with alcohol. The filtrates were combined and vacuum-evaporated. By distillation of the residue we obtained 5.06 g of N-acetyl-1-methylpentylamine, the properties and analysis of which are given in Table 2, A mixture of 4.2 g of N-acetyl-1-methylpentylamine and 50 ml of 3 N HCl was boiled for 90 min. After removal of the acid in a vacuum and drying of the residue we obtained 3.42 g of 1-methylpentylamine hydrochloride as a viscous oil. In the usual way from this hydrochloride we prepared the picrate, m.p. 123.5-124° after recrystallization from dilute alcohol, and the N-benzoyl derivative, m.p. 81.5-82.5°. The literature [25] gives m.p. 82-83°. Neither of these compounds melted with depression in admixture with the same 1-methylpentylamine derivative prepared otherwise (see above).

Preparation of N-Acetyl Derivatives of Alicyclic Amines by the Reductive Desulfurization of N-Acetyl Derivatives of Thiophene Amines

N-Acetyl-2-ethylcyclohexylamine (X; R = H, n = 3). About 70 g of Raney nickel was added to a solution of 9.3 g of 3-acetamide-2',3'-thiopheno-1,2-cyclohexane (IX; R = H, n = 3) in 250 ml of alcohol at 65°, and the mixture was then stirred at 65-70° for seven hours. Nickel was filtered off and washed with alcohol. The filtrates were combined and evaporated to dryness. The residue was dissolved in chloroform, and the solution was filtered and vacuum-evaporated. There remained 7.4 g of a substance of m.p. 103-108°, which, according to its analysis (see Table 2),

TABLE 1

Name of substance	B.p., °C (p, mm)	M.p., °C	n_D^{20}	Yield, %	Molecular formula	C, %		H, %		N, %		S, %	
						found	calc.	found	calc.	found	calc.	found	calc.
5-t-Butyl-2-thenylamine (II; R = t-C_4H_9, R' = H)*	120—122 (5)	—	1,5228	80	—	—	—	—	—	—		—	—
Picrate**	—	188—189	—	—	—	—	—	—	—	—	—	—	—
Acetyl derivative	—	76,5—77	—	77	$C_{11}H_{17}ONS$	62,46 62,69	62,55	8,07 8,04	8,11	6,37 6,51	6,63	15,16 15,33	15,18
α-Methyl-2-thenylamine*** (II; R = H, R' = CH_3)	74—100 (10)	—	1,5480	37	—	—	—	—	—	—	—	—	—
Picrate	—	182—185	—	—	$C_{12}H_{12}O_7N_4S$	40,72 40,42	40,45	3,39 3,45	3,39	15,85 16,00	15,72	8,92 8,81	8,99
Acetyl derivative****	147,5—149 (2)	70—71	—	96	—	—	—	—	—	—	—	—	—
Phenylsulfonyl derivative	—	72—73	—	85	$C_{12}H_{13}O_2NS_2$	53,75 53,88	53,92	4,81 4,87	4,92	5,90 5,82	5,24	23,67 23,72	23,98
3-Amino-2',3'-thiopheno-1,2-cyclohexane (VII; R = H, n = 3)	120—120,5 (10)	—	1,5790	82	$C_8H_{11}NS$	63,11 63,20	62,70	7,56 7,49	7,24	—	—	20,64 20,67	20,92
Picrate	—	230	—	—	$C_{14}H_{14}O_7N_4S$	44,16 44,09	43,98	3,78 3,73	3,69	14,61 14,49	14,65	8,25 8,34	8,39
Acetyl derivative	—	167—167,5	—	92	$C_{10}H_{13}ONS$	61,52 61,38	61,50	6,69 6,71	6,71	7,14 7,11	7,17	16,12 16,19	16,42
Phenylsulfonyl derivative	—	143—144	—	87	$C_{14}H_{15}O_2NS_2$	57,54 57,43	57,31	5,31 5,26	5,15	5,12 5,07	4,77	21,70 21,66	21,86
3-Amino-2',3'-thiopheno-1,2-cycloheptane (VII; R = H, n = 4)	126—128 (10)	—	1,5710	82	—	—	—	—	—	—	—	—	—
Picrate	—	205	—	—	$C_{15}H_{16}O_7N_4S$	45,61 45,70	45,45	4,29 4,26	4,07	14,14 14,20	14,14	8,01 8,04	8,09
Acetyl derivative (IX; R = H, n = 4)	—	178—179	—	90	$C_{11}H_{15}ONS$	63,00 63,02	63,12	7,11 7,31	7,22	6,44 6,48	6,69	15,32 15,12	15,32
Phenylsulfonyl derivative	—	131,5—132,5	—	86	$C_{15}H_{17}O_2NS_2$	58,75 58,76	58,60	5,51 5,45	5,57	4,86 4,91	4,56	20,86 20,87	20,86
3-Amino-5'-methyl-2',3'-thiopheno-1,2-cycloheptane (VII; R = CH_3, n = 4)	137—139 (9)	—	1,5610	85	$C_{10}H_{15}NS$	66,44 66,38	66,24	8,34 8,41	8,34	7,87 7,92	7,73	17,83 17,92	17,69
Picrate	—	214—215	—	—	$C_{16}H_{18}O_7N_4S$	47,14 47,16	46,82	4,46 4,43	4,42	13,70 13,89	13,65	7,81 7,65	7,81
Acetyl derivative (IX; R = CH_3, n = 4)	—	160,5—161	—	—	$C_{12}H_{17}NOS$	64,17 64,41	64,53	7,35 7,34	7,67	6,08 6,09	6,27	14,01 14,26	14,36

* The literature [14] gives: b.p. 75 – 82° (2 mm); n_D^{20} 1,5048 (for the unpurified substance).

** The literature [16] gives m. p. 185 – 186°.

*** The literature [17, 18] gives: b.p. 82.5 – 83° (14 mm); n_D^{15} 1,5582; b.p. 83 – 84° (16 mm).

**** The literature [19] gives m. p. 76 – 78°.

TABLE 2

Name of substance	B.p., °C (p, mm)	M.p., °C	n_D^{20}	Yield, %	Molecular formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.
Pentylamine picrate*	—	137—138	—	—	$C_{11}H_{16}O_7N_4$	41,95 41,90	41,78	5,12 5,08	5,10	17,71 17,78	17,72
N-Acetyl-6,6-dimethylheptylamine (IV; R = t-C_4H_9, R' = H)	129,5—130 (2)	—	1,4510	88	$C_{11}H_{23}ON$	71,26 71,11	71,29	12,64 12,37	12,51	7,60 7,53	7,56
Picrate	—	170—171	—	92	$C_{15}H_{24}O_7N_4$	48,68 48,63	48,38	6,27 6,46	6,50	14,83 14,93	15,06
1-Methylpentylamine (V; R = H, R' = CH_3)**	116—120 (760)	—	1,4145	40	—	—	—	—	—	—	—
Picrate	—	121,5—123	—	—	$C_{12}H_{18}O_7N_4$	43,62 43,41	43,64	5,48 5,60	5,49	16,81 16,86	16,96
Acetyl derivative	101—105 (1,5)	—	1,4425	70	$C_8H_{17}ON$	—	—	—	—	9,79 9,60	9,78
Benzoyl derivative***	—	81,5—82,5	—	56	$C_{13}H_{19}ON$	—	—	—	—	6,54 6,45	6,82
2-Ethylcyclohexylamine (mixture of cis and trans isomers; VIII; R = H, n = 3)	52—66 (15)	—	1,4608	50	—	—	—	—	—	—	—
Picrate (mixture of isomers)	—	193—196	—	82	$C_{14}H_{20}O_7N_4$	46,93 46,86	47,19	5,74 5,85	5,66	—	
trans-2-Ethylcyclohexylamine picrate****	—	198—199	—	—	$C_{14}H_{20}O_7N_4$	47,07 46,88	47,19	5,87 5,66	5,66	—	
cis-2-Ethylcyclohexylamine picrate*****	—	188—189	—	—	$C_{14}H_{20}O_7N_4$	47,34 47,26	47,19	5,71 5,52	5,66	—	

* The literature [23] gives: m.p. 139.5 – 140.5°.

** The literature [24] gives: b.p. 117 – 118°; b.p. 114 – 115°.

*** The literature [25] gives: m.p. 82 – 83°.

**** The literature [11] gives: m.p. 198 – 199°.

***** The literature [11] gives: m.p. 189°.

TABLE 2 (continued)

Name of substance	B.p., °C (p, mm)	M.p., °C	n_D^{20}	Yield, %	Molecular formula	C, %		H, %		N, %	
						found	calc.	found	calc.	found	calc.
N-Acetyl-2-ethylcyclohexyl-amine (mixture of isomers)	—	103	—	92	$C_{10}H_{19}ON$	71,25 70,93	70,96	11,39 11,16	11,31	8,60 8,63	8,28
trans-N-Acetyl-2-ethylcyclo-hexylamine	—	125—125,5	—	—	$C_{10}H_{19}ON$	70,97 70,99	70,96	11,05 11,29	11,31	8,34 8,32	8,28
Phenylsulfonyl derivative (mixture of isomers)	—	116—121	—	—	$C_{14}H_{21}O_2NS$	63,00 62,77	62,88	7,99 7,93	7,92	—	—
2-Ethylcycloheptylamine (mixture of isomers; VIII; R=H, n=4)	70—74 (10—11)	—	1,4705	49	$C_9H_{19}N$	76,51 76,41	76,52	13,39 13,36	13,56	— —	—
Picrate (mixture of isomers)	—	157—165	—	72	$C_{15}H_{22}O_7N_4$	48,86 48,57	48,64	5,80 5,79	5,99	15,27 15,24	15,13
Picrate (one isomer)	—	177—178	—	—	$C_{15}H_{22}O_7N_4$	48,75 48,50	48,64	5,78 5,75	5,99	14,92 14,84	15,13
Phenylsulfonyl derivative	—	107—108	—	—	$C_{15}H_{23}O_2NS$	64,05 64,24	64,02	8,22 8,19	8,24	5,23 5,12	4,98
N-Acetyl-2-ethylcycloheptyl-amine (mix. of isomers: X:R=H, n=4)	164—165 (10)	52—63	—	77	$C_{11}H_{21}ON$	72,35 72,14	72,08	11,51 11,64	11,55	7,74 7,74	7,64
N-Acetyl-2-ethylcycloheptyl-amine (one isomer)	—	75—77	—	—	$C_{11}H_{21}ON$	72,23 72,18	72,08	11,65 11,52	11,55	— —	—
N-Acetyl-2-propylcycloheptyl-amine (mixture of isomers; R=CH_3, n=4)	178—182 (10—12)	62—69	—	92	$C_{12}H_{23}ON$	72,73 72,64	73,04	11,79 11,96	11,75	7,40 7,35	7,10
N-Acetyl-2-propylcycloheptyl-amine (one isomer)	—	96—96,8	—	—	$C_{12}H_{23}ON$	73,12 73,03	73,04	11,62 11,67	11,75	— —	—

corresponded to N-acetyl-2-ethylcyclohexylamine and was a mixture of the cis and trans isomers. By the crystallization of this mixture from dilute alcohol we isolated a substance of m.p. 124-125° which melted without depression in admixture with the acetyl derivative of trans-2-ethylcyclohexylamine prepared from the picrate of this amine (see above).

11.8 g of the mixture of acetyl derivatives was boiled for four hr with 50 ml of 1 : 1 hydrochloric acid. The solution was cooled, and 150 ml of water was added. The precipitated oil was extracted with three 50-ml portions of benzene, solvent was distilled off, and the residue was dried in a vacuum desiccator. The oil obtained crystallized out on standing (8.9 g, m.p. 80-98°). By repeated crystallization of this substance from dilute alcohol we isolated trans-N-acetyl-2-ethylcyclohexylamine, m.p. 124.5-125°.

By evaporating the aqueous layer remaining after the benzene extraction we obtained 3.4 g of an oily substance (contaminated cis-2-ethylcyclohexylamine hydrochloride), which was dissolved in 30 ml of water. Sodium hydroxide was added to the solution until a turbidity appeared, and then a few drops of hydrochloric acid were added. To the resulting solution we added a warm alcoholic solution of 4.8 g of picric acid and then water until a turbidity appeared. The mixture was cooled, and the precipitate formed was filtered off and dried. We obtained 4.75 g of a picrate, m.p. 117-147°. It was boiled with 300 ml of ether, and the residue was filtered off and washed with ether (2.74 g, m.p. 188-189°). After recrystallization from dilute alcohol the melting point did not alter. Judging from the melting point the substance was cis-2-ethylcyclohexylamine picrate. The literature [11] gives m.p. 189°. For the analysis of the picrate of m.p. 189° see Table 2.

N-Acetyl-2-ethylcycloheptylamine (X; R = H, n = 4). About 70 g of Raney nickel was added to a solution of 10.5 g of 3-acetamido-2',3'-thiopheno-1,2-cycloheptane (IX; R = H, n = 4) in 350 ml of alcohol at 65°. Stirring at 65-70° was continued for 11 hr. Nickel was filtered off and washed with warm alcohol. Alcohol was vacuum-distilled off, the residue was dissolved in chloroform, and the solution was filtered from aluminum hydroxide. By vacuum fractionation of the filtrate we isolated 7 g of a fraction of b.p. 164-165° (10 mm), which solidified on standing and appeared to consist of a mixture of the acetyl derivatives of cis- and trans-2-ethylcycloheptylamines (see Table 2). By repeated crystallization of this mixture from hexane we isolated an isomer with a constant melting point of 75-77°. The analysis of this isomer is given in Table 2.

N-Acetyl-2-propylcycloheptylamine (X; R = CH_3, n = 4). About 70 g of Raney nickel was added to a solution of 7.0 g of 3-acetamido-5'-methyl-2',3'-thiopheno-1,2-cycloheptane (IX; R = CH_3, n = 4) in 250 ml of alcohol at 60°. The mixture was stirred at 65-70° for 17 hr, after which the solution gave a negative reaction for sulfur. The precipitate was filtered off and washed with alcohol. The filtrates were combined, and alcohol was vacuum-distilled off. The residue was dissolved in hot chloroform, the solution was filtered from aluminum hydroxide, and the filtrate was vacuum-evaporated. There remained 5.7 g of oil, which solidified on standing. The unpurified substance had m.p. 62-69° and appeared to consist of a mixture of the N-acetyl derivatives of cis- and trans-2-propylcycloheptylamines. The analysis of the mixture is given in Table 2. By crystallization of this mixture from hexane we isolated an isomer of m.p. 96-96.80 (see Table 2).

SUMMARY

A new method was developed for the preparation of primary aliphatic and alicyclic amines by the reductive desulfurization of oximes and amines containing a thiophene nucleus with the aid of Raney nickel.

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