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Studies on Sodium Novaminsulfonate

Sodium Novaminsulfonat (Novaljin) Üzerinde Araştırmalar

Hayriye AMÂL, Nedime ERGENÇ, İlkin SANLI and
Hilâl TOKATLI *

Sodium novaminsulfonate, which is one of the most popular analgesic agents used as tablet or injection in our country, is not stable especially in the form of solution. Generally in liquid heterogeneous systems, the active ingredient tends to decompose, and this fact in sodium novaminsulfonate (SNS).

It has been well known that the aqueous solution of SNS may acquire a yellow color. In DAB 7 (1) it is stated that in a freshly prepared solution no color should be produced within three minutes, and Pharmacopoea Helvetica (2) states that the color of a 20 % solution of SNS should not be deeper than an appropriate standart color solution.

The purity test for SNS in different pharmacopoeas based on the detection of some impurities and the determination of their limits; these impurities consist especially of phenazone, sulfamipyrine (melubrin), and 4-methylaminophenazone.

A survey in the literature showed that sodium novaminsulfonate in aqueous solution was decomposed to methylaminophenazone, and N,N'methylenebismethylaminophenazone. Awe and Tracht (3) prepared an aqueous solution of SNS and set aside for 4-6 weeks and extracted the dark yellow colored solution with chloroform, removed the solvent, and chromatographed on Al_2O_3 column and obtained the N,N'-methylenebismethylaminophenazone.

This paper presents the results of an investigation carried out with sodium novaminsulfonate and its injections obtained from different sources**

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* Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Istanbul.

** Novalgine (Siegfried), Sulpyrine (Daichi Seigaku and Panabe Feigaku), Metamizol (Boeringen, Jugelheim), Devalgine, Metalgine.

EXPERIMENTAL

Thin-layer chromatograhpy. 10 µl of each freshly prepared solution of about 30 mg SNS in 100 ml of methanol, and also a suitable amount of SNS injection were spotted on silica gel G plates. The plates were developed in chloroform-methanol (100:50) (d 1.250 at 24°), then dried with hot air and sprayed with a solution of 1 g p-dimethylaminobenzaldehyde in a mixture of 30 ml ethanol, 3 ml hydrochloric acid and 180 ml of n-butanol (4). Three yellow colored spots were obtained which have the Rf values 0.04, 0.37, and 0.62 respectively.

Column chromatography. Silica gel 0.2-0.5 mm (120 g, in a column of 4x60 cm) was used as adsorbant and 3 g of SNS in methanol was chrotmatographed, using chloroform-methanol (90:10). The first (60×30 ml) fractions showed only one spot on thin-layer (Rf 0.62). The solvent of combined fractions was evaporated in a rotatory evaporator, a yellow colored residue was obtained This product was washed first with ether, then with ethanol-ether mixture and crystallized from a small amout of ethanol. A creamy white crystalline powder was obtained, m.p. 159-160°. This substance was N, N'-methylenebismethylaminophenazone (substance A). The fractions 61-81 were not studied, because the yield was very small. The fractions 82-113 were concentrated in a rotatory evaporator, the residue was washed with chloroform and crystallized from ethanol. A white crystalline powder, m.p. 178-183° (dec.) (substance B) was obtained. When this compound was subjected to thin-layer chromatographic control, showed two spots having the Rf valvues of 0.04 and 0.37 respectively. The substance B was left aside for future studies.

N,N'-methylenebismethylaminophenazone. The UV absorption was examined by VSU 1 model Zeiss Spectrophotometer $\lambda^{EtOH}_{max.}$ 246 mµ (Σ 9 600), at 279 mµ, Sholder. IR sperctrum (KBr, Perkin-Elmer, model 137) 1681 Cm^{-1} (C=O); 1600 cm^{-1}, 1504 cm^{-1} and 1374 cm^{-1} (aromatic or heterocyclic ring); 1316 cm^{-1} (C_6H_5-N bond); 771 cm^{-1} and 702 cm^{-1} (monosubstituted phenyl).

NMR spectrum ($CDCl_3$, TMS as internal standard, Varian instrument, model A 60 A-) 2.15 ppm (C-CH_3 group in heterocyclic ring); 2.82 ppm (N-CH_3 in heterocyclic ring); 4.23 ppm (-N-CH_2-N-group in N,N'-methylenebismethylaminophenazone) and 7.28 ppm (δ) (proton in the benzen rings).

Reaction of N,N'-methylenebismethylaminophenazone with benzensulfonylchloride. A mixture of 400 mg of substance A and 0.8 ml benzensulfonylchloride was heated on a water bath and shaked for one-two minutes, 10 ml of a solution of 10 % sodium hydroxide was added; the mixture was shaken vigorously for 30 minutes, warmed to about 50-60°, shaken again and then cooled. From the cooled mixture, after having been allowed to stand for ten minutes, benzensulfonyl derivative separated out (5). The precipitate was collected by filtration, washed twice with 1 ml of water, then washed again with 5 ml of petroleum ether. The product was purified by crystallization from methanol. Shiny white plates, m.p. 132-134°, were chromatographed on silica gel HF_{254} thin-layer with a solvent system chloroform-methanol (100:50), Rf 0.70. This substance was the [N-methyl-phenazonyl-4]-benzensulfonamide.

Anal.- Calcd. for $C_{18}H_{19}N_3O_3S$: N, 11.76; S, 8.96. Found: N, 12.06; S, 8.99.

Hydrolysis of [N-methyl-phenazonyl-4]-benzensulfonamide. 400 mg of sulfonamide was treated with 1 ml of 80 % sulfuric acid, heated at 165° for fifty minutes allowed to cool, and treated with 20 % sodium hydroxide in order to liberate the free amine. From the alkaline solution, amine was extracted with ether and ether was evaporated (6) to yield a creamy white crystalline substance, namely 4-N-methylaminophenazone, m.p. 60-61°. It was chromatographed on silica gel G thin-layer comparing with the N,N'-methylenebismethylaminophenazone. They showed the same Rf value, 0.62.

Hydrolysis of sodium novaminsulfonate. 4.73 g SNS was refluxed with 20 ml of 10 % potassium hydroxide solution for about one hour. A dark orange solution was produced, cooled, extracted with chloroform. The chloroform extract was evaporated in a rotatory evaporator to give a yellowish crystalline substance which was washed with ether to yield a creamy white crystalline substance, m.p. 170° ;identic with substace A.

DISCUSSION

A freshly prepared methanolic solution of sodium novaminsulfonate (SNS) and SNS injections were chromatographed on silica gel G plates and three spots having different Rf values were detected with p-dimethylaminobenzaldehyde reagent. In order to separate these three substances a silica gel column was used. The N,N'-methylenebismethylaminophenazone (Rf 0.62) obtained from the first sixty (30 ml each) fractions was examined by UV, IR, and NMR spectroscopy. The findings were shown in Table I.

Table I

The characteristic abs. values of N,N'-methylenebismethylamnophenazone in UV, IR and NMR

UV	IR	NMR
246 mμ	1681 Cm^{-1} (C=0)	2.15 ppm ($C\text{-}CH_3$)
279 mμ (a shoulder)	1600, 1504 and 1374 Cm^{-1} (aromatic or heterocyc. ring)	2.82 ppm ($N\text{-}CH_3$ in heterocyc. ring)
		4.23 ppm ($\text{-}N\text{-}CH_2\text{-}N\text{-}$)
	1316 Cm^{-1} ($C_6H_5\text{-}N$ bond)	7.28 ppm (proton in C_6H_5 rings)
	771 and 702 Cm^{-1} (mono substitut. phenyl)	

The UV absorptions (λmax.) of some ohter pyrazolone derivatives which were used for comparison were shown in Table II.

Table II

Aminopyrine	Phenazone	Sulfamipyrine	Sodium novaminsulfonate
272 mμ	269 mμ	255 mμ	265 mμ
238 mμ	243 mμ		235 mμ

As it is seen from the IR bands, there is no-SO_3Na band in N,N'-methylenebismethylaminophenazone (substance A) whereas

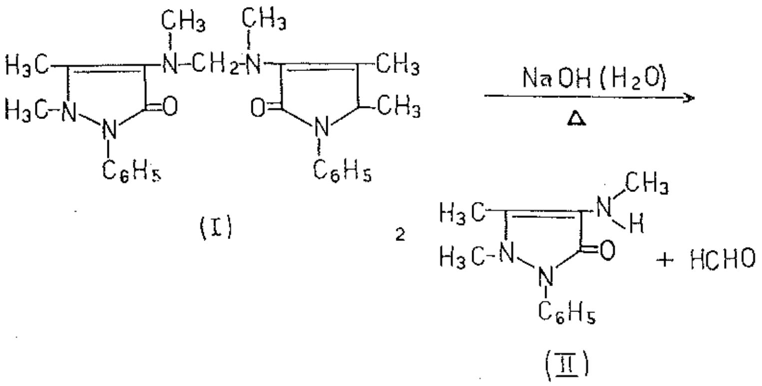
C_6H_5-N, and carbonyl bands are present. NMR bands show the presence of -N-CH_2-N- group of the substance A, and the -CH_2-SO_3Na band which is found in sodium novaminsulfonate is not present in the NMR spectrum of substance A.

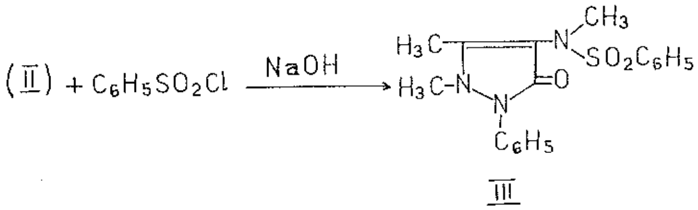
The substance B obtained from the second fractions of column chromatography (fractions 82-113) was a mixture of SNS and small amounts of a substance which was not yet identified.

The -N-CH_2SO_3Na group of SNS was hydrolysed and the hydrolysate was controlled on silica gel G plates by comparing with SNS and substance A. The results showed that in aqueous solutions the amount of substance A, formed by hydrolysis, was increased with the heating period.

RESULTS and CONCLUSION

The substance A obtained from the first fractions of the column chromatographic separation of sodium novaminsulfonate was the N,N'-methylenebismethylaminophenazone (I) and contained, a small amount of 4-N-methylaminophenazone (II). These two substances showed the same Rf values on silica gel thin-layer, and have the melting points 170° (3) and 63° (7) respectively. The melting point of substance A was found 160°. A small amonut of 4-N-methylaminophenazone depressed the melting point of N,N'-methylenebismethylaminophenazone. The -N-CH_2-N- group of substance A was shown by NMR spectrum. The UV and IR spectra of substance A confirmed the above mentioned structure. On the other hand, the reaction product of substance A with benzensulfonyl chloride showed the same melting point of benzensulfonyl derivative of 4-N-methylaminophenazone (8). Elementary analysis, IR spectra and some chemical reactions showed that this was the [N-methyl-N-phenazonyl-(4)]-benzensulfonamide (III). While the sulfonization reaction was carried out in the presence of NaOH, the methylenebis-derivative was split out to the 4-N-methylaminophenazone, and this substance reacted with benzensulfonylchloride to give the sulfonamido derivative of the secondary amine. [N-Methyl-N-phenazonyl-(4)]benzensulfonamide was hydrolysed with 80% sulfuric acid and a substance was obtained with a melting point 60-62° (4-N-methylaminophenazone).





In this investigation a freshly prepared, colorless methanolic solution of SNS was used, and directly chromatographed on silica gel column. Each fraction was checked on thin-layer and those which gave the same spots were combined. Chemical reactions, melting point, UV, IR and NMR spectra showed that the first substance was N,N'-methylenebismethylaminophenazone with traces of 4-N-methylaminophenazone. All attempts to separate N-methylaminophenazone from methylenebis derivative was failed. As a result, it was seen that sodium novaminsulfonate contains different amounts of substance A even in solid form, and this amount increases in aqueous solutions.

Sodium novaminsulfonates used in this study were obtained from different sources, and it was seen that the amount of substance A was different in each SNS sample. The authors will continue to study the estimation of the substance A in various sodium novaminsulfonates and also its preparations.

SUMMARY

A freshly prepared methanolic solution of sodium novaminsulfonate gave three spots on silica gel G thin-layer, In order to separate these three spots a freshly prepared methanolic solution of SNS was chromatographed on silica gel (0.2-0.5 mm) column and eluted with chloroform-methanol (90:10). The first fractions (60×30 ml) which showed only one spot on thin-layer were combined and the solvent was evaporated in a rotatory evaporator, a yellow colored substance was obtained. It was recrystallized from ethanol to give o creamy white crystalline substance, namaly N,N'-methylenebismethylaminophenazone, m.p. 159-160° The chemical structure of these substance was determined by using UV, IR and NMR spectroscopic methods. This substance was also treated with benzensulfonylchloride in the presence of NaOH, and obtained a white crystalline compound, m.p. 132°. The elementary analysis, UV and IR spectra and some chemical reactions showed that this was the [N-methyl-N-phenazonyl-(4)]-benzensulfonamide. N,N'-methylenebismethylaminophenazone was converted to 4-N-methylaminophenazone in the presence of NaOH, and this 4-N-methylaminophenazone reacted with benzensulfonylchloride to produce the benzensulfonamide derivative of secondary amine group of the substance. On the other hand, sodium novaminsulfonate was hydrolysed with 20 % KOH and N,N'-methylenebismethylaminophenazone (m.p. 170°) was obtained. As a result, it was seen that sodium novaminsulfonates obtained from different sources contained different amount of N,N'-methylenebismethylaminophenazone and a small amount of 4-N-methylaminophenazone, even in solid form.

ÖZET

Sodium novaminsulfonatın (novaljin) metanollü çözeltileri silica gel G tabakaları üzerinde üç tane leke meydana getirmektedir. Yeni hazırlanmış metanollü bir çözelti silica gel (0.2-0.5 mm) sütunundan kromatografiye edildiğinde, ilk 60 fraksiyon ince tabakada bir tek leke meydana getirmiş ; birleştirilen fraksiyonlardan çözücü, alçak basınçta uçurulduktan sonra, sarı renkli bir madde elde edilmiş ve alkolden billûrlandırılan maddenin yapısı tâyin edilmiştir. Erime derecesi, UV, IR ve NMR spektrumları bu

maddenin N,N'-metilenbismetilaminofenazon olduğunu göstermiştir. Maddenin benzensulfonil klorür ile elde edilen türevinin [N-methyl-N-fenazonil-(4)]-benzensulfonamid yapısında olduğu, erime derecesi, elemanter analiz, UV ve IR spektrumları yardımı ile gösterilmiştir. Benzen sulfonilklorür ile reaksiyon NaOH karşısında yürüdüğü için, önce NaOH, metilen bis türevini 4-N-metilaminofenazon haline geçirmekte ve bu sonucu madde de sulfonamid türevini meydana getirmektedir. Novaljin içerisinde gerek katı halde, gerekse hidroliz sonucunda teşekkül etmiş olarak, N,N'-metilenbismetilaminofenazon bulunduğunu göstermek için novaljin KOH ile hidroliz edilmiş ve erime derecesi 170° olan, her hususta novaljinden sütun kromatografisi yardımı ile alınan maddeye uyan bileşik elde edilmiştir. Sonuç olarak, çeşitli kaynaklardan temin edilmiş olan novaljinler içinde, katı halde dahi, N,N'-metilenbismetilaminofenazon ve az miktarda N-metilaminofenazon bulunduğu ve bu iki maddenin kromatografik yollarla birbirinden ayrılamadığı tespit edilmiştir.

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