

SYNTHESIS OF 1-(ACETYLSALICYLYL)- BENZOTRIAZOLE AND ITS REACTION WITH POLYVINYL ALCOHOL

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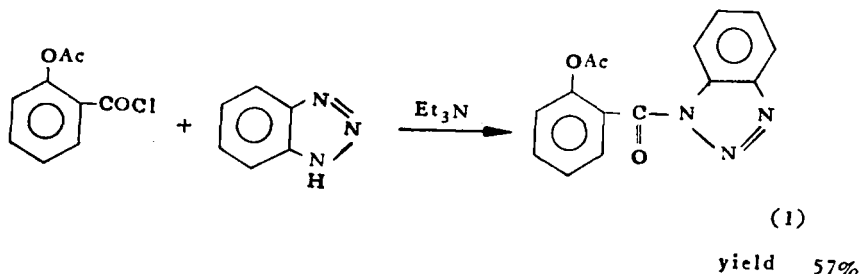
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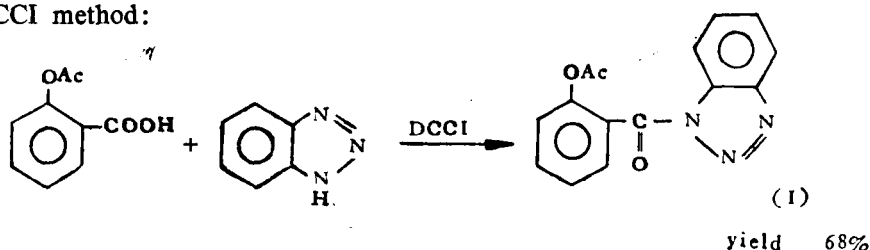
1-(Acetylsalicylyl)-benzotriazole, a new active amide of acetylsalicylic acid has been synthesized either from acetylsalicylic acid and benzotriazole using DCCI as condensation agent or via acetylsalicylyl chloride and benzotriazole in the presence of triethylamine. The obtained active amide reacted readily with the hydroxyl group of PVA to produce the acetylsalicylyl ester of PVA.

Polyvinyl alcohol (PVA) hydrogels have been used as biocompatible biomaterials^[1]. Acetylsalicylic acid (aspirin) is a well-known analgesic and antipyretic drug, recently, its anticoagulation effect on blood platlet has been discovered and varified. But only little effort has been diverted to the macromolecularization of aspirin for preparing the corresponding polymeric drugs^{[2][3]}. We have synthesized five new acrylic monomers containing aspirin-moiety in the ester group, and then have them polymerized radically^{[4][5]}. From the hydrolysis behavior of these polymers it is reasonable to consider them as the candidates of some controlled release biocompatible materials to liberate aspirin by prolonged hydrolysis^[6]. By introducing aspirin moieties into the PVA side chains through the reaction of polymer modification, it would give some new biomedical hydrogels. Referring to the work of Noma et al. to introduce the benzyl groups to PVA side chains via benzyl chloride with rather high yield^[7], we have tried to introduce the acetylsalicylyl groups to PVA via acetylsalicylyl chloride. But only some dark-brown colored products resulted and the further purification proved difficult. Therefore, we turned to synthesize the active amide of acetylsalicylic acid, 1-(acetylsalicylyl)benzotriazole (ASBA) (I), which would introduce the acetylsalicylyl group to PVA chains very smoothly. Two methods of synthesis of acetylsalicylylbenzotriazole were used as follows:

Acid chloride method:



DCCI method:



EXPERIMENTAL

Acetylsalicylyl chloride was synthesized as described previously^[2]

1-(Acetylsalicylyl)benzotriazole (ASBA)

Acid chloride method^[8]: To a stirred solution of 20 g (0.1 mol) acetylsalicylyl chloride in 100 ml dry benzene, a solution of 12 g (0.1 mol) benzotriazole and 10.1 g (0.1 mol) triethylamine dissolved in 150 ml dry benzene was added dropwisely over 2 hr at 0–5°C. The mixture was then reacted at room temperature for 4 hr. The triethylamine hydrochloride salt was filtered out and the filtrate was condensed by rotatory evaporator. The crude product was recrystallized with THF–petroleum ether (1:3), 16.1 g of white needle crystal was obtained with yield 57%, m.p. 102–104°C.

DCCI method^[8]: To a stirred solution of 9.0 g (0.05 mol) acetylsalicylic acid in 100 ml THF, 6.0 g (0.05 mol) benzotriazole was added, and followed by 10.3 g (0.05 mol) dicyclohexylcarbodiimide (DCCI). The mixture was reacted at 0–3°C for 2 hr and then at room temperature for 2 hr. The dicyclohexylurea was filtered out. The filtrate was condensed to obtain the crude product which was purified as described above. The yield was 68%.

Reaction of ASBA with PVA: In a representative procedure, to the solution of 0.63 g (0.13 mol) PVA (D.P.1700) in 20 ml DMSO, 0.88 g (0.003 mol) of ASBA was added and followed by 0.35 g (0.035 mol) of triethylamine. The mixture was stirred at 60°C for 40 hr, and then poured into ice–water (0–2°C) to precipitate the product. After filtration, the product was obtained and then extracted with methylisobutylketone for 24 hr. After having been immersed in ice–water for 24 hr, the product was dried at 60°C under vacuum, 1.1 g of the colorless product yielded.

RESULTS AND DISCUSSION

A new active amide of acetylsalicylic acid, ASBA was synthesized by two ways, i.e. acid chloride method and DCCI method. The yield of DCCI method is higher.

ASBA is in colorless needle crystal form with melting point 102–104°C.

Elementary analysis of ASBA:

Calcd. for $C_{15}H_{11}N_3O_3$: C%, 64.01 H%, 3.91 N%, 14.91

Found: C%, 63.98 H%, 3.95 N%, 14.91

IR (cm^{-1} , KBr): 1605 (phenyl); 1710 ($\nu_{\text{C=O}}$ ester group); 1760 ($\nu_{\text{C=O}}$ —C(=O)—NH—).



Fig. 1 and Fig. 2 show the ^1H -NMR and mass spectra of ASBA respectively

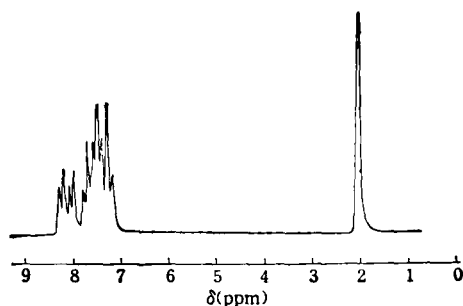


Fig. 1 ^1H -NMR of 1-(acetylsalicylyl)benzotriazole δ (ppm, 80 MHz, CDCl_3); 2.05 (s, 3H, $\text{CH}_3\text{—CO—}$), 7.25, 7.35, 7.45, 7.58, 7.76, 7.85, 8.10, 8.30 (m, 8H, ortho-substituted phenyl).

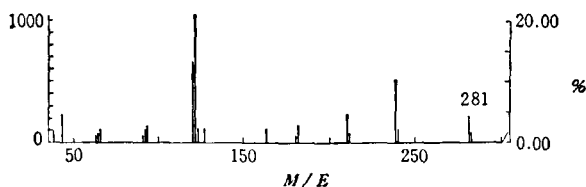


Fig. 2 Mass spectra of 1-(acetylsalicylyl)benzotriazole (15 eV)
Molecular weight: Calcd. for $(\text{C}_{18}\text{H}_{11}\text{N}_3\text{O}_3)_n$; Found 281.

From the elementary analysis, molecular weight by mass spectra, IR and NMR spectra, the structure of this active amide obtained from acetylsalicylic acid and benzotriazole was confirmed as represented in (I).

The solubility behavior of ASBA was summarized in the Table 1.

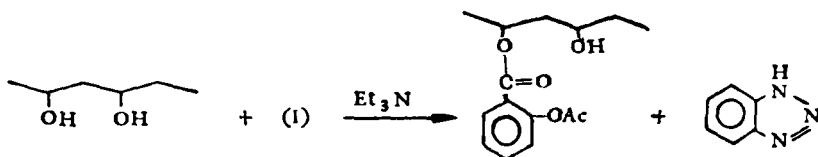
Table 1 Solubility of ASBA

Solvent	Solubility	Solvent	Solubility
cyclohexane	insol.	methanol	sol.
hexane	insol.	ethanol	sol.
petroleum ether	insol.	acetone	sol.
benzene	sol.	tetrahydrofuran	sol.
dioxane	sol.	dimethylsulfoxide	sol.
chloroform	sol.	dimethylformamide	sol.

insol.: insoluble, sol.: soluble.

Reaction of ASBA with PVA:

Acetylsalicylyl group was introduced into the PVA chains via its active amide form ASBA, smoothly.



Different degrees of acetylsalicylation could be achieved by varying the reaction conditions, i.e. ASBA/PVA ratio and reaction temperature, and the reaction is controllable. Table 2 summarized the reaction condition on the degree of acetylsalicylation of the reaction of ASBA with PVA.

Table 2 Reaction condition on the degrees of acetylsalicylation

No.		1	2	3	4
Reaction condition	PVA / ASBA (mol)	4	4	1	4
	Et ₃ N / ASBA (mol)	1.1	1.1	1.1	none
	Temp. (°C)	room temp.	60	60	60
	Time (hr)	48	48	48	48
Product	Elementary analysis (C%)	57.44	58.43	58.27	56.18
	Yield (%)	98.2	99.1	83.6	39.1
	Acetylation (%)	59.1	79.3	76.1	33.3
	In acetone	sol.	sol.	sol.	sol.

Fig. 3 shows the IR spectra of reaction product of ASBA with PVA (PVA-ASA, bulk line) and that of PVA (dotted line).

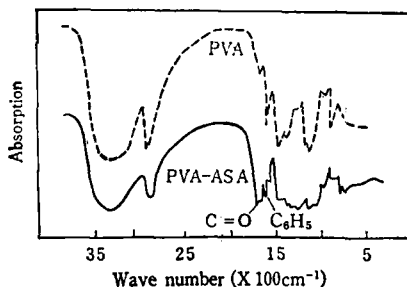


Fig. 3 IR of the reaction product of ASBA with PVA

PVA: dotted line;

PVA-ASA: bulk line.

The presence of 1620 cm^{-1} band due to phenyl group and 1730 cm^{-1} band due to ester group clearly shows that the acetylsalicyl group has been introduced into PVA chains.

The solubility behavior of PVA-ASA is just opposite to PVA itself, i.e. insoluble in H_2O but soluble in methanol.

Besides 271 nm band of acetylsalicyl group in UV spectra of PVA-ASA, the appearance of 303 nm band of salicylic acid indicated that some deacetylation occurred during the reaction. This was proved by the fact that if the product was treated with acetic anhydride and pyridine^[9] to convert into aspirin moieties, 303 nm band in UV spectra would no longer appear.

Further studies on the properties of the polyvinyl alcohol ester having aspirin moieties are in progress.

REFERENCES

- [1] Usakov, B. N., Trukhmanova, L. B., Drozdova, E.V., Markelova, T. M., Dokl. Akad. Nauk SSSR **1961**, 141, 1117; *Chem. Abstr.*, **1962**, 56, 12795.
- [2] Vogl, O., Tirrell, D., *Macromol. Chem.*, **1980**, 181, 2097; *J. Polym. Sci.*, **1980**, 18 (9), 2755.
- [3] Eckert, T., Zander, M., *Arch. Pharm.*, **1977**, 310 (2), 136; *Chem. Abstr.*, **1977**, 86, 188747.
- [4] 李福绵、顾忠伟、冯新德, 科学通报, **1981**(17), 1054.
- [5] 李福绵、顾忠伟、冯新德, 高分子通讯, **1981**(5), 395.
- [6] 顾忠伟、李福绵、冯新德, 科学通报, **1982**(16), 988.
- [7] Noma, K., Nakamura, S., Teramura, J., *Kobunshi Kagaku*, **1947**, 4, 41.
- [8] Ferruti, P., Angelino, F., Giovanni, C., *J. Polym. Sci., Polym. Chem. Ed.*, **1974**, 12, 553; *ibid.*, **1974**, 12, 2453.
- [9] McDowell, W. H., Kenyon, W. O., *J. Am. Chem. Soc.*, **1940**, 62, 415.