

Mannich Reaction of 1-*n*-Butyl-3-*p*-tosylurea. I. Syntheses of 3-*n*-Butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine and 3,5-Di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine

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1-*n*-Butyl-3-*p*-tosylurea (tolbutamide) does not incorporate the secondary amines, piperidine, diethylamine, dimethylamine, dipropylamine, pyrrolidine and morpholine, to any significant extent in its normal Mannich reaction under alkaline conditions in refluxing methanol, acetonitrile and dioxane. Instead 3-*n*-butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine and 3,5-di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine are mainly formed usually in good yields. These triazines have been isolated and characterized, and a mechanism is proposed for their formation.

Key words 1-*n*-butyl-3-*p*-tosylurea; triazine; Mannich reaction; cyclization; alkaline condition; *p*-toluenesulfonamide

Urea undergoes the Mannich reaction with one and two equivalents of morpholinomethanol to give mono- and dimorpholinomethylureas respectively.¹⁾ Urea in which one amide hydrogen atom has been substituted does not react with morpholinomethanol. Mono- and dimorpholinomethylurea can also be prepared by reacting para-formaldehyde, morpholine and urea in dioxane.

Many substrates structurally similar to urea have been aminomethylated, *e.g.*, tetrahydro-2-(1*H*)-pyrimidine,²⁾ 2,4-(1*H*,3*H*)-pyrimidinedione,²⁾ sulfones,^{3–5)} and *p*-toluenesulfonamide.⁶⁾ 1,3-Dimethylsulfuryldiamide (**1**), another substrate similar to urea, gives 1,2,4,6-thiatriaza-cyclohexane-1,1-dioxide (**2**) in the Mannich reaction with formaldehyde and primary amines.

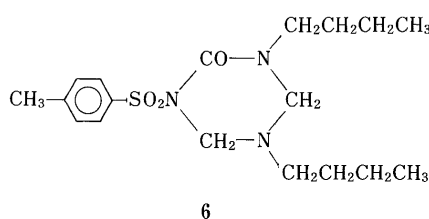
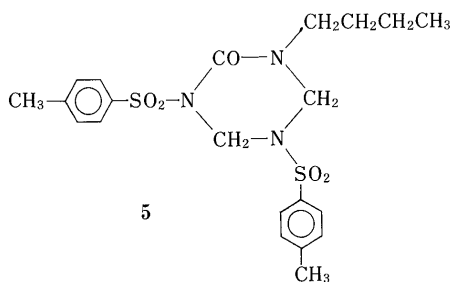
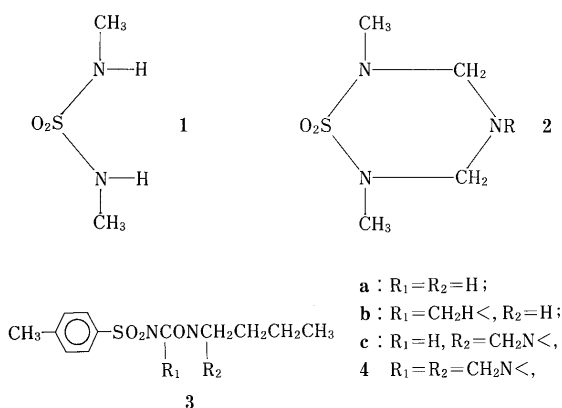
We tried to synthesize simple mono-aminomethylated (**3b**, **3c**), diaminomethylated (**4**) derivatives of 1-*n*-butyl-3-*p*-tosylurea (tolbutamide, **3a**) under alkaline conditions

using secondary amines in order to improve the pharmacologic and pharmacokinetic properties of this important hypoglycemic agent. However these simple mono- and diaminomethylated derivatives were not formed under alkaline conditions using formalin and various secondary amines at room temperature or in refluxing methanol, tetrahydrofuran (THF), dioxane or acetonitrile. Instead, we isolated as the major products, and for the first time, 3-*n*-butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine (**5**) and 3,5-di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine (**6**). These results shed light on the mechanism of the Mannich reactions of amides in general and sulfonylureas in particular.

Here we describe the isolation and characterization of these triazines and propose a mechanism for their formation.

Results

Tolbutamide failed to give simple mono- and diamino-methyl derivatives incorporating secondary amines under alkaline and slightly alkaline conditions at room or reflux temperature in methanol, ethanol, THF, dioxane or acetonitrile with aqueous formaldehyde. Unexpectedly, triazines were the major products. These triazines have been isolated, characterized and identified as 3-*n*-butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine (**5**) and 3,5-di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine (**6**). These cyclic Mannich bases were formed in yields of 18% and 61% respectively, when an equimolar mixture of 40% aqueous formaldehyde, tolbutamide and morpholine was heated at 60 °C for 3 h in methanol.



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A third product was also obtained in a trace amount. This has been isolated, characterized and identified as *N*-morpholinomethyl-*p*-toluenesulfonylcarbamic acid. Other secondary amines give the corresponding aminomethylated carbamic acids. Compound **6** was always formed at a faster rate than **5** and the formation of **5** and **6** is faster in acetonitrile than in methanol, THF, ethanol or dioxane. The formation of **5** and **6** is acid-catalyzed. But a mixture of secondary amine, aqueous formaldehyde and tolbutamide acidified with HCl to a pH of 1.00 did not give the triazines in refluxing methanol after 6 h. With hydrochloride salts of secondary amines, little or none of compound **5** was formed. An increase in the proportion of the secondary amine also led to a decrease in the amount of **5** and an increase in the amount of **6**. The rate of formation of **6** increased depending on the amine in this order: morpholine > dimethylamine > piperidine (or pyrrolidine). Compound **5** can be synthesized by reacting tolbutamide with formaldehyde and *p*-toluenesulfonamide in the presence of a secondary or tertiary amine. Similarly compound **6** can be synthesized by reacting tolbutamide with formaldehyde and *n*-butylamine in the presence of a secondary or a tertiary amine.

Discussion

As shown in Chart 1, the hydrolysis of tolbutamide under basic conditions can follow two pathways, A and B. Pathway A give a sulfonamide (IA) and a carbamic

acid (IIA), while pathway B gives *N*-(*p*-toluenesulfonyl)carbamic acid (IB) and *n*-butylamine (IIB). As usual, the rate of this hydrolysis is a function of the pH of the medium, and the temperature. The pH of the medium will depend on the solvent, the pK_a and the concentration of the reactant amine. Tolbutamide is more stable to hydrolysis at acidic pH. Compounds IA, IIA, IB and IIB are intermediates whose reactivities and concentrations determine the rates of the subsequent reactions.

The unhydrolyzed molecules of tolbutamide in slightly alkaline medium are converted into their dianion (III) by the loss of two protons to unprotonated amine molecules. The resulting dianion (III), which is a much stronger nucleophile than both the protonated and unprotonated amine molecules, reacts with two equivalents of formaldehyde to give the bis-methylol (IV). This condenses with a molecule of sulfonamide (IA), producing the triazine **5**, or with *n*-butylamine, producing the other triazine **6**. Primary amines undergo this condensation reaction more readily than primary sulfonamides and amides, which are more reactive than the secondary amines, probably for steric reasons. Secondly, the cyclic Mannich bases may be more stable than their acyclic counterparts in the case of tolbutamide. These facts probably explain why secondary amines are hardly incorporated into the Mannich bases. These triazines have been isolated and, based on their yields, pathway B appears to predominate under slightly alkaline and neutral conditions. Compounds IIA, IIB, IB

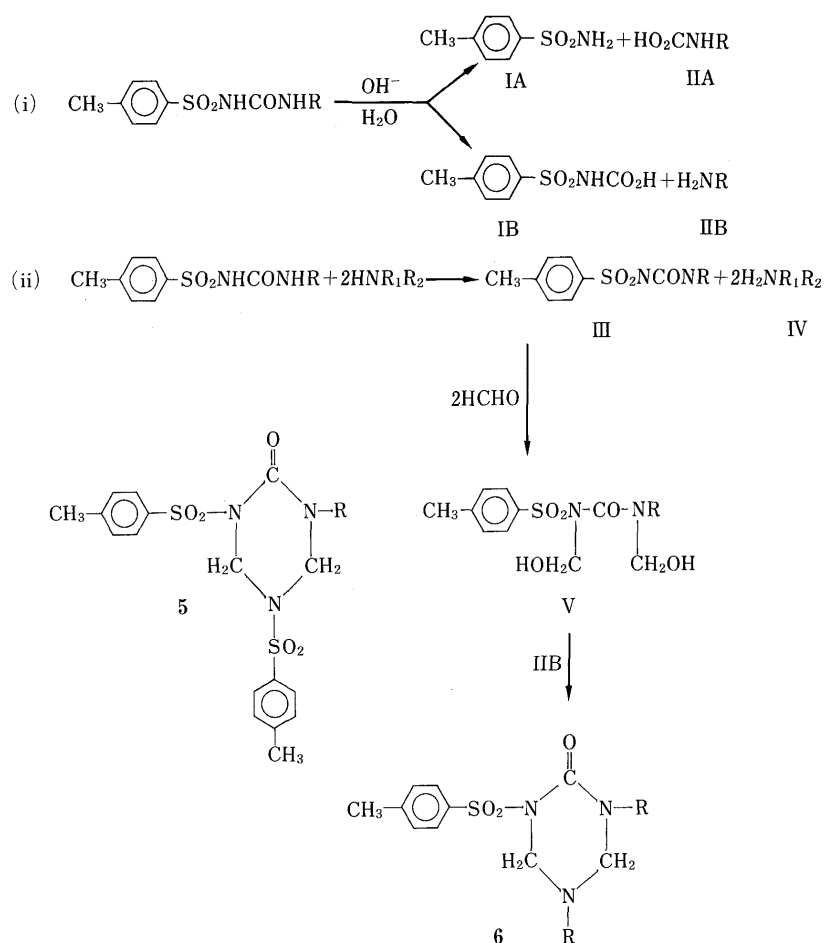


Chart 1

and the Mannich base of IB have been isolated by column chromatography and identified. Little or no **5** is obtained under acidic conditions or with the hydrochloride salt of the amine, probably because tolbutamide is more stable to hydrolysis under acid conditions. Further the formation of the dianion (III) will not be possible. This type of formaldehyde cyclization has been applied to the syntheses of 5- and 6-membered heterocycles.⁷⁻¹⁰

These triazines were isolated by column chromatography and identified primarily on the basis of their spectral data, particularly ¹H-NMR. In DMSO-*d*₆, the -CONHCH₂- triplet at δ 6.45 and the broad -CONHSO₂- singlet at δ 15.00, seen in the spectrum of the parent **3a**, are lost. This indicates the absence of the two amide hydrogen atoms in tolbutamide. The following additional peaks (given in δ values) are consistent with the structure **5**: 4.25 (4H, s, NCH₂N-), 7.45 (4H, d, Ph-H). It is noteworthy that the Ph-CH₃, (δ 2.40) peak integrates for six protons instead of three in tolbutamide. This supports the presence of two *p*-toluenesulfonyl groups in **5**. Compound **6** has a similar spectrum with some modifications in the chemical shifts and intensities of the peaks. For instance, the δ 0.81—1.00 CH₃ peak integrates for six protons while the -CH₂- peak (δ 1.00—1.70), integrates for eight protons. Here the four -NCH₂N- protons appear as two two-proton singlets. This can be attributed to the anisotropic effects of the -SO₂- and -CO- groups. The presence of δ 0.80—1.00 multiplet and the δ 1.00—1.50 multiplet strongly indicates that the tolbutamide chain is intact in **5** and **6**.

Experimental

Apparatus The 90 MHz NMR spectra were recorded on a varian VXR-300 spectrometer using DMSO-*d*₆ as the solvent and Me₄S as the internal standard. The elemental analysis, IR and mass spectrometry were performed at the Chemistry Department of the University of Wales College of Cardiff.

Materials Tolbutamide, aqueous formaldehyde (40%), hexane, ethyl acetate, CaCl₂ (anhydrous), diethylamine, 1-*n*-butyl-3-*p*-tosylurea (tolbutamide), dimethylamine, dibutylamine, pyrrolidine, piperidine, morpholine, butylamine and *p*-toluenesulfonamide were all obtained from Sigma Chemical Co., U.S.A. They were all of analytical grade and were used without further purification. Silica gel 60, F₂₅₄ on aluminum sheet, and neutral, F₂₅₄ aluminum oxide on aluminum sheet were obtained from Merck, Darmstadt, while silica gel grade 60, 230—400 mesh and aluminum oxide, grade I, F₂₅₄ were obtained from Aldrich Chemical Co., Ltd., England.

Attempted Syntheses of Simple Aminomethyl Derivatives (Mannich Bases) of 1-*n*-Butyl-3-*p*-tosylurea (3b**, **3c** and **4**)** Methanol (40 ml) was placed in a flask, and either 2.4 ml (0.016 mol) or 4.8 ml (0.032 mol) of morpholine and 4.0 g (0.016 mol) of tolbutamide were added. When the tolbutamide was dissolved, 1.6 ml (0.016 mol) or 3.2 ml (0.032 mol) of aqueous formaldehyde was added in three aliquots. The flask was firmly closed each time and heated at 60 °C for 1 h. Ethanol, THF, dioxane and acetonitrile were tried as solvents. Other secondary amines, namely dimethylamine, diethylamine, dipropylamine, piperidine, and pyrrolidine, as well as their HCl salts were tried in various molar proportions. The reaction was also attempted at room temperature, under acid catalysis and at various pH values. The reaction mixture was subjected to TLC using ethyl acetate-hexane (3:2) or toluene-ethyl acetate (3:1) on Silica gel 60.

Isolation of 3-*n*-Butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine (5**)** Compound **5** was eluted together with **6** using ethyl acetate-hexane (3:2) over alumina (activity I). The solvent was removed under pressure after the solution was dried over anhydrous CaCl₂. The mixture solidified on scratching the flask vigorously. Compound **5** was next eluted with

diethylamine-hexane (1:2) over alumina. It was recrystallized from MeOH-H₂O mixture and dried at 40 °C under vacuum. Yield, 18%. ¹H-NMR (DMSO-*d*₆) δ : 0.70—1.00 (3H, m, CH₃), 1.10—1.50 (4H, m, CH₂-), 2.15—2.45 (2H, t, -NCH₂N-), 2.50 (6H, s, PhCH₃), 4.30 (4H, s, NCH₂N), 7.45 (4H, d, Ph-H), 7.75 (4H, d, Ph-H). MS (*m/z*): 454 (M⁺), 451, 225, 183, 155, 91, 84, 64, 58. IR (KBr): 1690—1700 (C=O), 3480 (CONHSO₂) absent; 3125—3250 (CONH) absent; 1500—1650 cm⁻¹ (amide II band) absent. Microanalysis: Found: N=9.03 (8.87),^a C=54.19 (54.40),^a H=5.81 (5.71),^a mp 130—131 °C; Recryst. solvent: EtOH-H₂O (leaflets). Compound **5** is insoluble in aqueous NaOH, NaHCO₃ and in EtOH (absolute). *a*) The figures in brackets are theoretical values.

Isolation of 3,5-Di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine (6**)** Compound **6** was eluted with MeOH after **5** had been eluted. It was recrystallized from EtOH-H₂O. Yield, 61%; mp 68—69 °C. ¹H-NMR (DMSO-*d*₆) δ : 0.80—1.00 (6H, m, CH₃), 1.00—1.50 (8H, m, CH₂), 2.40 (3H, s, Ph-CH₃), 2.35—2.70 (2H, t, NCH₂), 2.90—3.20 (2H, t, NCH₂), 4.25 (2H, s, NCH₂N), 4.95 (2H, s, NCH₂N), 7.35—7.60 (2H, d, Ph-H), 7.80—8.05 (2H, d, Ph-H). MS (*m/z*): 367 (M⁺). Microanalysis: Found: N=11.24 (11.44),^a C=59.10 (58.85),^a H=8.11 (7.90),^a; Compound **6** is insoluble in aqueous NaOH and NaHCO₃. *a*) The figures in brackets are theoretical values.

Synthesis of 3-*n*-Butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine from *p*-Toluenesulfonamide A mixture of 100 ml of methanol, 8.0 g (0.032 mol) of tolbutamide and 9.6 ml (0.064 mol) of dimethylamine was stirred until the tolbutamide was completely dissolved. Then 6.4 ml (0.064 mol) 40% aqueous formaldehyde was added and the whole was stirred for 30 min. Finally 5.48 g (0.032 mol) of *p*-toluenesulfonamide was added and the solution was stirred for another 1 h. 3-*n*-Butyl-2-oxo-1,5-di-*p*-tosyl-perhydro-1,3,5-triazine (11.7 g) was eluted with EtOAc on alumina. Other secondary amines can be used in the place of dimethylamine. The physical and chemical characteristics are the same as reported for **5** that was isolated from the reaction mixture.

Synthesis of 3,5-Di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine using *n*-Butylamine A mixture of 100 ml of methanol, 13 ml (0.12 mol) of *n*-butylamine and 10 g (0.04 mol) of tolbutamide was stirred until the tolbutamide dissolved completely. Then 8 ml (0.08 mol) of 40% aqueous formaldehyde was added and the whole was stirred for 1 h. The reaction was followed by TLC using EtOAc-hexane (2:3) over silica gel. 3,5-Di-*n*-butyl-2-oxo-1-*p*-tosyl-perhydro-1,3,5-triazine (17.2 g) was eluted with EtOAc on alumina. The physical and chemical properties are the same as those reported for **6** isolated from the reaction mixture.

Isolation of *N*-Morpholinomethyl-*p*-toluenesulfonylcarbamic Acid This was isolated by repeated column chromatography. Compounds **5** and **6** were first eluted with EtOAc over alumina. *N*-Morpholinomethyl-*p*-toluenesulfonylcarbamic acid was eluted next with EtOAc over silica gel. ¹H-NMR (DMSO-*d*₆) δ : 2.3 (3H, s, Ph-CH₃), 3.0 (4H, t, CH₂N), 3.3 (4H, t, CH₂O), 3.45 (2H, s, NCH₂N), 7.45 (2H, d, Ph-H), 7.75 (2H, d, Ph-H).

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References

- 1) Weaver W. I., Simons J. K., Baldwin W. E., *J. Amer. Chem. Soc.*, **66**, 2204 (1944).
- 2) Sidzhakova D., Danchev D., Galabov A. S., Volichkova E., Karparov A., *Archiv. der Pharmazie.*, **315**, No. 6, 509—514 (1982).
- 3) Messinger R., Gompertz J., *Arch. Chem.*, **310**, 249 (1977).
- 4) Bohme H., Clement B., *Tetrahedron Lett.*, **20**, 1737—1740 (1979).
- 5) Stetter H., Steinbeck K., *Justus Liebigs Ann. Chem.*, **1315**, 174 (1968); *idem*, *J. Pharm. Sci.*, **57**(5), 715—733 (1968).
- 6) Bundgard H., Johansen M., *Int. J. Pharmaceutics.*, **7**, 129—136 (1980).
- 7) Hiramitsu T., Maki Y., *Synthesis*, **1977**, 177.
- 8) Elias G. P., Jones R. J., *J. Chem. Soc.*, **1**, 903 (1974).
- 9) Gene B. J., Snow M. R., Springberg J., Herltz A. J., Sargeson A. M., Taylor D. J., *J. Chem. Comm.*, **1976**, 285.
- 10) Harsanyi K., Kiss P., Korbonitis D., *J. Heterocycl. Chem.*, **10**, 435 (1973).