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NUCLEOPHILIC SUBSTITUTION, DEMETHYLATION AND METHYLATION IN HETEROCYCLIC SERIES

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Abstract—The products resulting from the condensation of potassium sulphanilamide and 3-methoxy-6-benzylsulphonylpyridazine have been investigated. In a reaction mixture consisting of N^1-methylsulphanilamide, N^1,N^1-dimethylsulphanilamide, 6-benzylsulphonyl-3-pyridazinone (VI) and 3-sulphanilamido-6-benzylsulphonylpyridazine (VII), demethylation, methylation and nucleophilic substitution takes place. The synthesis of VI and VII accomplished by an alternative route confirmed their structures.

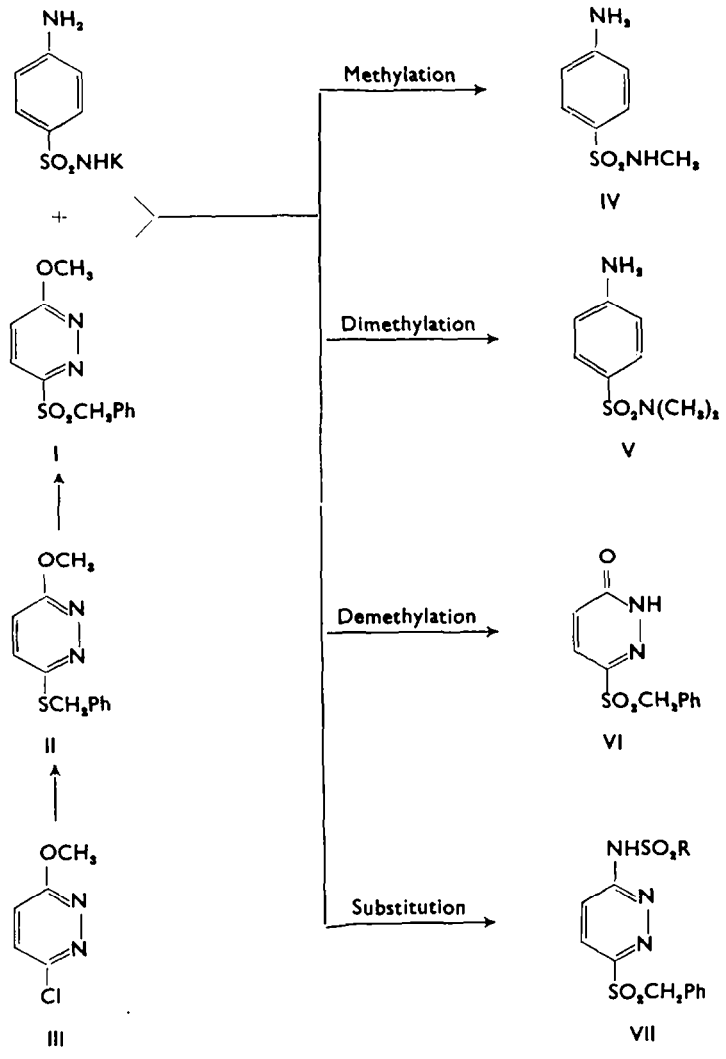
AS AN extension of the nucleophilic substitution of the benzylsulphonyl group by sulphanilamide anion in the pyrimidine series,[1] an attempt was made to prepare 3-sulphanilamido-6-methoxypyridazine—a therapeutically useful sulpha drug—by the interaction of 3-methoxy-6-benzylsulphonylpyridazine (I) and sulphanilamide anion. This reaction however, yields a mixture of four products, identified as N^1-methylsulphanilamide (IV), N^1,N^1-dimethylsulphanilamide (V), 6-benzylsulphonyl-3-pyridazinone (VI) and 3-sulphanilamido-6-benzylsulphonylpyridazine (VII). Since compounds VI and VII have not been described in the literature, it was necessary to confirm their structure by independent synthesis.

The synthesis of VII was achieved by oxidation and subsequent hydrolysis of 3-(*p*-acetylsulphanilamido)-6-benzylthiopyridazine (XIII). Acetylation of 3-sulphanilamido-6-benzylthiopyridazine (IX; prepared from VIII) resulted in the formation of an N^1-acetyl derivative X and also an N^4-acetyl product XIII. The structure of XIII was established by synthesis from 3-amino-6-benzylthiopyridazine (XII) and N^4-acetylsulphanilyl chloride. Compound XII was obtained by condensation of 3-amino-6-chloropyridazine (XI) and sodium benzylmercaptide. Preparation of VI was accomplished either by demethylation of 3-methoxy-6-benzylsulphonylpyridazine (I) with hydrochloric acid or by oxidation of 3-hydroxy-6-benzylthiopyridazine with performic acid. 3-Methoxy- and 3-hydroxy-6-benzylthiopyridazine were prepared from the corresponding 6-chloro derivatives by condensation with sodium benzylmercaptide.

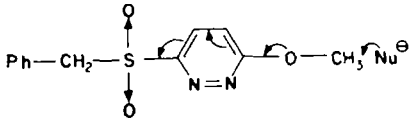
It is apparent that during the interaction of I and sulphanilamide anion demethylation, methylation and nucleophilic substitution take place. These reactions can be interpreted in terms of the effects of substituted and substituting groups. The reactivity of 3,6-disubstituted derivatives of pyridazine has been discussed by Shepherd *et al.*[2] who also suggest a similar mechanism of reactions. Demethylation of I and

[1] S. Kukolja and Z. Cvetnić, *Croat. Chem. Acta* **34**, 115 (1962).
[2] R. G. Shepherd, W. E. Taft and H. M. Krazinski, *J. Org. Chem.* **26**, 2764 (1961).

Chart I

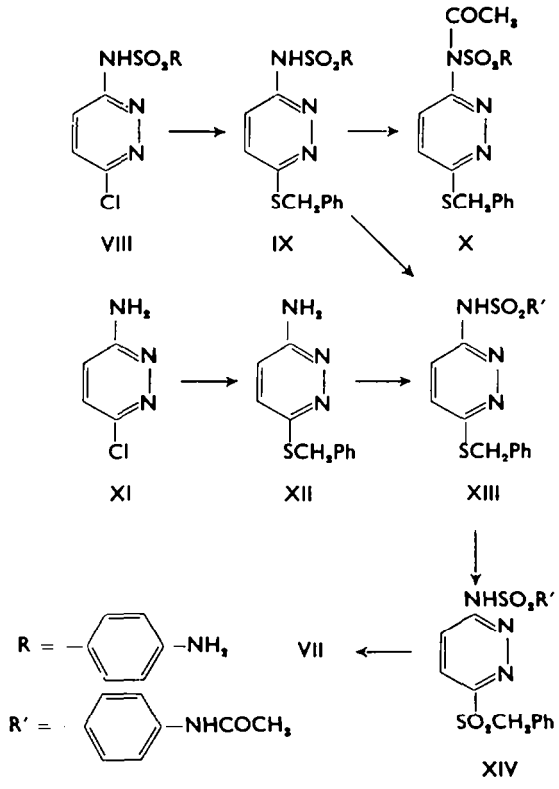


methylation of sulphanilamide anion may be illustrated as proceeding from a structure such as:



where Nu^- is the sulphanilamide anion. In this electronic structure both substituents are conjugated with each other through the pyridazine ring. The methyl group is activated by the electrophilic benzylsulphonyl group and hence the methyl-oxygen fission occurs, which leads simultaneously to demethylation and methylation. According to Shepherd *et al.*,[2] this is a general reaction of heterocyclic methoxy groups,

Chart II



especially in the presence of certain electrophilic substituents on the heterocyclic ring. Clark *et al.* obtained a fairly good yield of methoxy substituted product (3-sulphanilamido-6-methylsulphonylpyridazine) with only a small amount of methylsulphonyl substituted and somewhat less of demethylation products.[3] In the present case, the yield is somewhat lower, presumably as a consequence of a lower reactivity of the methoxyl toward substitution.

EXPERIMENTAL

3-Methoxy-6-benzylthiopyridazine (II)

To a solution of sodium methoxide, prepared from 13·3 g (0·58 g atom) sodium and 300 ml dry methanol, 72 g (0·58 mole) benzylmercaptan was added. After evaporation of methanol (red. press.) a solution of 84 g (0·58 mole) 3-chloro-6-methoxypyridazine[4] in 450 ml dry toluene was added and this mixture refluxed for 4·5 hr, cooled and filtered. The solvent was distilled leaving a viscous residue which solidified upon cooling and was washed with water and dried in a desiccator for 4 days, yield 120·2 g (89%), m.p. 80–82°. Recrystallization from dimethylformamide–water (1:1) yielded colourless crystals, m.p. 83–84°, (Found: C, 61·84; H, 4·94; N, 11·79. $C_{12}H_{12}N_2OS$ requires: C, 62·06; H, 5·21; N, 12·06%).

[3] We thank R. G. Shepherd for informing us, in a private communication, about these results. See also ref. 9 in cit. 2.

[4] J. Druey, Kd. Meier and K. Eichenberger, *Helv. Chim. Acta* **37**, 121 (1954).

3-*Methoxy-6-benzylsulphonylpyridazine* (I)

A mixture of 30 g (0·143 mole) 3-methoxy-6-benzylthiopyridazine, 520 ml formic acid, 65 ml water and 75 ml 30% hydrogen peroxide was kept in a refrigerator overnight. The product was filtered off, washed with water and dried, yield 23·4 g, m.p. 138–141°. After crystallization from alcohol colourless crystals (15·7 g, 41%, m.p. 144–146°) were obtained. Further recrystallization gave crystals m.p. 146–147°, (Found: C, 54·84; H, 4·40; N, 10·44. $C_{12}H_{12}N_2O_3S$ requires: C, 54·54; H, 4·58; N, 10·60%).

3-*Amino-6-benzylthiopyridazine* (XII)

The preparation was carried out with 4·47 g (0·194 g atom) sodium, 100 ml methanol, 24 g (0·194 mole) benzylmercaptan, 25·1 g (0·194 mole) 3-amino-6-chloropyridazine[4] and 150 ml dimethylformamide by refluxing for 7 hr as described for II. After standing overnight the separated sodium chloride was removed by suction, 250 ml water added to the filtrate and the crude product filtered off, yield 40·5 g, m.p. 103–111°. Recrystallization from 360 ml 50% ethanol afforded 30·2 g (71%) colourless crystals, m.p. 99–101°. This compound was characterized by acetylation with acetic anhydride in acetic acid to give the crystalline 3-acetamido-6-benzylthiopyridazine, m.p. 190–191°, (Found: C, 59·96; H, 4·87; N, 15·91. $C_{13}H_{13}N_3OS$ requires: C, 60·22; H, 5·05; N, 16·21%).

3-(N⁴-*acetylsulphanilamido*)-6-*benzylthiopyridazine* (XIII)

Procedure A. 8·85 g (0·04 mole) 3-amino-6-benzylthiopyridazine was added to 25 ml dry pyridine followed by 7·5 g (0·032 mole) N-acetylsulphanyl chloride. After standing 2 days at room temp, the mixture was adjusted to pH 5 with dil. hydrochloric acid, then 50 ml water added and the mixture kept overnight in a refrigerator. The precipitate was filtered off and after drying weighed 12·2 g, m.p. 166–168°. It was crystallized from alcohol, yielding 5·6 g (33%), m.p. 178–180°. A sample was recrystallized from alcohol for analysis, m.p. 182–183°, (Found: C, 55·04; H, 4·17; N, 13·56. $C_{19}H_{18}N_4O_3S_2$ requires: C, 55·07; H, 4·38; N, 13·52%).

Procedure B. A mixture of 14·8 g (0·04 mole) 3-sulphanilamido-6-benzylthiopyridazine, 28 ml glacial acetic acid and 18 ml acetic anhydride was refluxed for 45 min and then kept at room temp overnight. The resulting solid (5·2 g, m.p. 192–195°), undoubtedly a mixture of N¹- and N⁴-acetyl derivatives, was removed by suction. To the filtrate 50 ml water was added and the solution kept at room temp for a further 2 hr. A second crop (10·4 g, m.p. 162–165°) of solid was filtered off. The first crop (5·2 g) was added to 20 ml 0·75 N sodium hydroxide and heated to 50°. Undissolved product (3·0 g, m.p. 197–199°) was filtered off and the filtrate acidified with acetic acid to pH 5. The separated solid was removed by suction, washed and dried yielding 1·3 g N⁴-acetyl derivative, m.p. 182–183°. The second crop (10·4 g) was treated in a similar manner. The total yield of crude N¹-acetyl derivative, insoluble in the sodium hydroxide solution was 4·0 g, and of N⁴-acetyl derivative (soluble in the solution of sodium hydroxide) was 10·6 g. A small sample was recrystallized from alcohol. The product m.p. 182–183° proved to be identical with the product obtained under A. The analytical sample m.p. 203–204° is N¹-acetyl derivative X, (Found: C, 55·22; H, 4·13; N, 13·33. $C_{19}H_{18}N_4O_3S_2$ requires: C, 55·07; H, 4·38; N, 13·52%).

3-(N⁴-*Acetylsulphanilamido*)-6-*benzylsulphonylpyridazine* (XIV)

Compound XIII (46·3 g; 0·11 mole) was oxidized with performic acid as described for I. The yield was 33 g (66%) colourless crystals m.p. 227–229°. Recrystallization from 50% alcohol yielded an analytical sample m.p. 229–231° (Found: C, 50·96; H, 3·81; N, 12·16. $C_{19}H_{18}N_4O_5S_2$ requires: C, 51·12; H, 4·06; N, 12·55%).

3-*Sulphanilamido-6-benzylsulphonylpyridazine* (VII)

Procedure A. A mixture of 8·4 g (0·04 mole) potassium salt of sulphanilamide, 5·25 g (0·02 mole) 3-methoxy-6-benzylsulphonylpyridazine and 80 ml dimethylsulphoxide was heated at 140–150° for 5 hr. after which time dimethylsulphoxide was evaporated (red. press.) The residue was dissolved in 50 ml water by heating and the solution adjusted with conc. hydrochloric acid to pH 8. After keeping in a refrigerator overnight the unreacted material (6·8 g, m.p. 144–150°) was filtered off, the filtrate acidified to pH 5 and cooled. Filtration and drying afforded 2·1 g (25%) of a product, m.p. 188–196°. Three recrystallizations from aq. ethanol yielded the sample for analysis, m.p. 216–217°, (Found: C

50·74; H, 4·19; N, 13·79. $C_{17}H_{16}N_4O_4S_2$ requires: C, 50·50; H, 3·99; N, 13·79%). A mixed m.p. with a sample obtained as described under B showed no depression.

The acidic filtrate was investigated by paper chromatography according to the procedure of Shepherd *et al.*,[3] and the presence of five compounds was detected namely, 3-sulphanilamido-6-benzylsulphonylpyridazine (R_f 0·33), sulphanilamide (R_f 0·52), 6-benzylsulphonyl-3-pyridazinone (R_f 0·64), N^1-methylsulphanilamide (R_f 0·76) and N^1, N^1-dimethylsulphanilamide (R_f 0·86). After this qualitative data, quantitative determinations on the acidic filtrate were carried out. The filtrate was evaporated to dryness (red. press.) and the residue extracted with 150 ml absolute alcohol and 2·05 g of an insoluble inorganic material obtained. Evaporation of alcohol yielded 3·09 g of a tarry product, which was extracted with 200 ml chloroform and 1·17 g of unreacted sulphanilamide obtained. The chloroform extract was evaporated, the residue dissolved in 10 ml water and filtered. The aliquote part of this solution was chromatographed on Whatman paper (thick 4 mm, 10 × 23 cm). After cutting and extracting the determined zone 0·116 g of N^1-methylsulphanilamide, 0·05 g N^1, N^1-dimethylsulphanilamide and 0·015 g 6-benzylsulphanyl-3-pyridazinone were obtained.

Procedure B. A solution of 20 g (0·045 mole) XIV in 100 ml 2·5 *N* sodium hydroxide was refluxed for 2 hr. After cooling it was acidified with dil. hydrochloric acid to pH 5, cooled and the resulting solid filtered off, washed and dried yielding 9·5 g, m.p. 190–195°. By crystallization from alcohol 5·2 g (29%), m.p. 215–216·5°, R_f 0·33 was obtained, which gave no depression of m.p. when mixed with a specimen prepared as described above under A.

3-*Sulphanilamido-6-benzylthiopyridazine* (IX)

Procedure A. Prepared by hydrolysis of 2·0 g XIII as described for VII under B. The crude product 1·8 g (97%) was recrystallized from alcohol yielding an analytical sample, m.p. 191–193°, (Found; C, 55·03; H, 4·56; N, 14·92. $C_{17}H_{16}N_4O_2S_2$ requires: C. 54·84; H, 4·33; N, 15·05%).

Procedure B. Prepared from 42·9 g (0·15 mole) 3-sulphanilamido-6-chloropyridazine[4] and sodium benzylmercaptide as described for II. The crude product (79·3 g) was crystallized from a mixture of dimethylformamide–water (1:1), yielding 32 g (57%), m.p. 191–193°, identical with the product obtained by procedure A.

3-*Hydroxy-6-benzylsulphonylpyridazine* (VI)

Procedure A. 2·0 g of I and 20 ml conc. hydrochloric acid was refluxed for 20 hr, cooled and filtered; yield 1·8 g, m.p. 210–211°. Recrystallization from water yielded an analytical sample, m.p. 210–211°, R_f 0·64, (Found: C, 52·52; H, 3·82; N, 11·23. $C_{11}H_{10}N_2O_4S$ requires: C, 52·80; H, 4·05; N, 11·20%).

Procedure B. By oxidation of 10 g (0·046 mole) 3-hydroxy-6-benzylthiopyridazine with performic acid as described for I, yielding 7·9 g, m.p. 209–211° and no depression with a mixed specimen.

3-*Hydroxy-6-benzylthiopyridazine*

Prepared from 39 g (0·3 mole) of 3-hydroxy-6-chloropyridazine[4] and sodium benzylmercaptide as described for II. The product (52 g, m.p. 140–150°) was recrystallized from dil. alcohol, yielding 33·2 g. A sample was recrystallized twice for analysis, m.p. 159–161°, (Found: C, 60·68; H, 4·45; N, 12·83. $C_{11}H_{10}N_2OS$ requires: C, 60·54; H, 4·62; N, 12·84%).

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