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# Sulfonamides Acting on the Central Nervous System, VI[1)]

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A series of 2-(acylamino)benzenesulfonamides was prepared. Their anti-convulsant effects on two convulsives (electro-shock and pentetrazol) were studied. The structure/effect relationships were compared with those of a series of isomeric 2-aminobenzenesulfon-N-acylamides and of 2-nitrobenzenesulfon-N-acylamides. The possible influence of $pK_a$ and log P was examined.

**Sulfonamide mit Wirkung auf das Zentralnervensystem, 6. Mitt.**

Es wurde eine Reihe von 2-Acylaminobenzolsulfonamiden synthetisiert und ihre antikonvulsive Wirkung untersucht (Elektroschocktest, Pentetrazolschock). Die Struktur-Wirkung-Beziehungen wurden im Vergleich zu einer Reihe von isomeren 2-Aminobenzolsulfon-N-acylamiden und von

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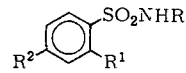
2-Nitrobenzolsulfon-N-acylamiden betrachtet. Der Einfluß, den zwei physikalisch-chemische Parameter, der pKa und der Log P, darauf ausüben können, wurde untersucht.

In course of research in sulfonamides acting on the central nervous system, and with specific reference to a series of 2-acylaminobenzenesulfonamides unsubstituted at the benzene ring and with anti-convulsant properties (pentetrazol), the authors had succeeded in demonstrating the importance of the nature of the acyl-group present in the molecule[2]. Accordingly, in subsequent research in this field, it was decided to investigate the influence exerted by another factor, namely, the presence of substituents at the benzene ring.

We therefore prepared the compounds **1–10** and investigated their effect on two convulsants (electro-shock and pentetrazol); the substituents at the benzene ring, as well as the acyl-group, were chosen with a view to establish a useful comparison with a series of isomeric compounds, the 2-aminobenzenesulfon-N-acylamides **11–19**, which had been the subject of a previous study[1].




| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| 1 | H | $NHCOCH(CH_3)_2$ | H |
| 2 | H | $NHCOCH(CH_3)_2$ | $CH_3$ |
| 3 | H | $NHCOCH(CH_3)_2$ | $CF_3$ |
| 4 | H | $NHCOCH(CH_3)_2$ | $OCH_3$ |
| 5 | H | $NHCOCH(CH_3)_2$ | Cl |
| 6 | H | $NHCOCH(C_2H_5)_2$ | H |
| 7 | H | $NHCOCH(C_2H_5)_2$ | $CH_3$ |
| 8 | H | $NHCOCH(C_2H_5)_2$ | $CF_3$ |
| 9 | H | $NHCOCH(C_2H_5)_2$ | $OCH_3$ |
| 10 | H | $NHCOCH(C_2H_5)_2$ | Cl |
| 11 | $COCH(CH_3)_2$ | $NH_2$ | H |
| 12 | $COCH(CH_3)_2$ | $NH_2$ | $CH_3$ |
| 13 | $COCH(CH_3)_2$ | $NH_2$ | $CF_3$ |
| 14 | $COCH(CH_3)_2$ | $NH_2$ | $OCH_3$ |
| 15 | $COCH(C_2H_5)_2$ | $NH_2$ | H |
| 16 | $COCH(C_2H_5)_2$ | $NH_2$ | $CH_3$ |
| 17 | $COCH(C_2H_5)_2$ | $NH_2$ | $CF_3$ |
| 18 | $COCH(C_2H_5)_2$ | $NH_2$ | $OCH_3$ |
| 19 | $COCH(C_2H_5)_2$ | $NH_2$ | Cl |
| 20 | $COCH(CH_3)_2$ | $NO_2$ | H |
| 21 | $COCH(CH_3)_2$ | $NO_2$ | $CH_3$ |
| 22 | $COCH(CH_3)_2$ | $NO_2$ | $CF_3$ |
| 23 | $COCH(C_2H_5)_2$ | $NO_2$ | H |
| 24 | $COCH(C_2H_5)_2$ | $NO_2$ | $CH_3$ |
| 25 | $COCH(C_2H_5)_2$ | $NO_2$ | $CF_3$ |

Since dissociation constant and lipophilia are thought to play a very important part in determining the anti-convulsant effect of sulfonamide derivatives[3,4,5], we decided to evaluate the pka and log P both of the compounds **1–19** and of some 2-nitroderivatives (compounds **20–25**)[1], from which certain 2-aminobenzenesulfon-N-acylamides can be derived, in order to obtain useful information regarding the influence exerted by the two parameters in these series of compounds.

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## Experimental Part

### Chemical

The procedure for the preparation of compound **6** was as described by a member of our team[6]; compounds **11–25** were prepared by the method described in[1].

*Preparation of the 2-acylaminobenzenesulfonamides* **1–5; 7–10**

These compounds were derived from the corresponding 2-aminobenzenesulfonamides by reaction with the appropriate acid-chloride in N,N-dimethyl-acetamide, following the procedure already laid down for other 2-acylaminobenzenesulfonamides[2]. All products were crystallised from acetone and petrol ether, b.p. 80–100 °C. The analytical data, yields and melting points are set out in Table 1.

*Determination of pka and log P*

The pka values were calculated by means of titration and UV spectroscopy.

The partition coefficients, expressed as log P and corrected for ionisation, were determined by means of high-pressure liquid chromatography according to *Unger* et al.[8], using a Perkin Elmer Mod. 601

**Table 1:** *2-Acylaminobenzenesulfonamides* **1–5** *and* **7–10**

| Compounds Nr. | Formula | Analysis[a] | Yield % | mp, °C[b] |
|---|---|---|---|---|
| 1[c] | $C_{10}H_{14}N_2O_3S$ | (C, H, N, S) | 83 | 117 |
| 2 | $C_{11}H_{16}N_2O_3S$ | (C, H, N, S) | 88 | 117 |
| 3 | $C_{11}H_{13}F_3N_2O_3S$ | (C, H, N, S) | 92 | 173–174 |
| 4 | $C_{11}H_{16}N_2O_4S$ | (C, H, N, S) | 84 | 126–127 |
| 5 | $C_{10}H_{13}ClN_2O_3S$ | (C, H, Cl, N, S) | 88 | 113 |
| 7 | $C_{13}H_{20}N_2O_3S$ | (C, H, N, S) | 91 | 139–140 |
| 8 | $C_{13}H_{17}F_3N_2O_3S$ | (C, H, N, S) | 92 | 130 |
| 9 | $C_{13}H_{20}N_2O_4S$ | (C, H, N, S) | 74 | 94 |
| 10 | $C_{12}H_{17}ClN_2O_3S$ | (C, H, Cl, N, S) | 89 | 149 |

[a] Analyses indicated by elemental symbols were within ± 0.25 of the theoretical values.

[b] MP: uncorr.

[c] Already prepared using a different procedure[7].

chromatograph (Perkin Elmer Mod. LC 55 UV-spectrophotometric detector, Rheodyne Mod. 7105 injection valve, ODS Sil-X-J column (25 × 0.26 cm), previously saturated with n-octanol). The range of the mobile phase (acetate buffer pH 3.6 saturated with n-octanol) was set at 1.0 ml/min and chromatographic analysis conducted at 25°C, the peaks being recorded at 254 nm. The samples in question were dissolved in the mobile phase and/or in a minimum quantity of acetonitrile and injected into the chromatograph in such quantities as would facilitate UV-readings and produce peaks of comparable areas. The two sets of results are set out in Columns 9 and 10, resp., of Table 2.

**Table 2:** *Anti-convulsant effects (M. E. S.), pka and log P of compounds* **1–25**

| Compound | Mol.wt. | Dose mm/kg i.p. | M.E.S. | | pKa | log P |
|---|---|---|---|---|---|---|
| | | | Anticonvulsant activity % protection[a] | % Mortality[a] | | |
| 1 | 242.3 | 0.264 | 25 (4) | 0 (4) | 9.50 | 0.97 |
| 2 | 256.3 | 0.390 | 17 (6) | 0 (6) | 9.56 | 1.45 |
| 3 | 310.3 | 0.322 | 0 (4) | 25 (4) | 8.98 | 2.45 |
| 4 | 272.3 | 0.367 | 0 (4) | 25 (4) | 9.60 | 1.37 |
| 5 | 276.7 | 0.361 | 0 (4) | 0 (4) | 9.46 | 1.87 |
| 6 | 270.3 | 0.555 | 17 (6) | 83 (6) | 9.40 | 1.62 |
| 7 | 284.4 | 0.088 | 0 (4) | 0 (4) | 9.51 | 2.13 |
| | | 0.176 | 38 (8) | 0 (8) | | |
| 8 | 338.3 | 0.295 | 0 (4) | 0 (4) | 9.02 | 3.06 |
| 9 | 300.4 | 0.186 | 38 (8) | 0 (8) | 9.48 | 2.01 |
| 10 | 304.8 | 0.328 | 0 (4) | 25 (4) | 9.50 | 2.55 |
| 11 | 242.3 | 0.413 | 17 (6)[b] | 100 (6)[b] | 5.22 | 1.17 |
| 12 | 256.3 | 0.390 | 25 (4)[b] | 25 (4)[b] | 5.44 | 1.65 |
| 13 | 310.3 | 0.322 | 50 (8)[b] | 25 (8)[b] | 4.75 | 2.56 |
| 14 | 272.3 | 0.367 | 0 (4)[b] | 50 (4)[b] | 5.47 | 1.58 |
| 15 | 270.3 | 0.370 | 0 (4)[b] | 25 (4)[b] | 5.29 | 1.64 |
| 16 | 284.4 | 0.352 | 0 (6)[b] | 17 (6)[b] | 5.38 | 2.18 |
| 17 | 338.3 | 0.295 | 25 (4)[b] | 25 (4)[b] | 4.76 | 3.04 |
| 18 | 300.4 | 0.333 | 25 (4)[b] | 25 (4)[b] | 5.42 | 2.03 |
| 19 | 304.8 | 0.328 | 0 (4)[b] | 0 (4)[b] | 5.10 | 2.53 |
| 20 | 272.3 | 0.257 | 0 (4)[b] | 50 (4)[b] | 3.78 | 1.72 |
| 21 | 286.3 | 0.258 | 0 (4)[b] | 25 (4)[b] | 4.04 | 2.17 |
| 22 | 340.3 | 0.294 | 80 (5)[b] | 20 (5)[b] | 2.84 | 3.10 |
| 23 | 300.3 | 0.203 | 0 (4)[b] | 0 (4)[b] | 4.14 | 2.17 |
| 24 | 314.4 | 0.267 | 0 (4)[b] | 25 (4)[b] | 4.36 | 2.67 |
| 25 | 368.3 | 0.271 | 80 (5)[b] | 20 (5)[b] | 3.18 | 3.57 |
| MP | | 2 µl/10 g | 0 (16) | 25 (16) | | |

a) Number of treated animals in brackets; b) Data may be deduced from[1]

**Pharmacology**

*Materials and methods*

The anti-convulsant activity of the 2-acylaminobenzenesulfonamides **1–10** was assessed in relation to convulsions induced both by maximal electro-shock (M. E. S.) and by the administration of pentetrazol (P. T. Z.). In both cases, the experimental procedure was as described in the previous paper[1]. The substances were invariably injected intraperitoneally at the various doses shown(+) (Table 2) and at the fixed vol. of 2 µl of N-methyl-2-pyrrolidone (M. P.) per 10 g of bodyweight. No parameter examined after administration of P. T. Z. was significantly modified by pre-treatment with the substances used. The results pertinent to the protection against the convulsive activity of maximal electroshock (M. E. S.) are set out in Table 2.

(+) For both convulsives the compounds were administered at equal doses.

**Results and Discussion**

Of all 2-acylaminobenzenesulfonamides examined, only **7** and **9** afforded partial protection against the convulsive activity of maximal electro-shock (M. E. S.); in both cases, 5 out of 8 rats were subject to convulsions while the mortality rate was zero. Since all the animals in the control group exhibited convulsions, the anti-convulsant effect of the substances is thereby demonstrated; however, no such firm conclusion can be reached regarding their anti-mortality effect, since only 4 out of 16 controls died.

It should also be pointed out that the anticonvulsant effect of compound **7** is exerted only at the dose of 0.176 mmol/kg; when the dose is halved, the effect disappears.

As regards the structure/effect relationships, it was found that methyl- and methoxy-substitution at the benzene ring (compounds **7** and **9**) were those that had a significantly positive effect on M. E. S.; however, this effect also depends on the nature of the acyl-group present in the molecule, for the corresponding lower homologues **2** and **4** were inactive even at doses twice as high as those of the diethylacetyl-derivatives **7** and **9**.

Comparing now the series of 2-acylaminobenzenesulfonamides **1–10** with the isomeric 2-aminobenzenesulfon-N-acylamides **11–19** and with certain 2-nitro-derivatives **20–25** from which the latter are derived, it can be seen that the influence of the substituents present at the benzene ring is not univocal throughout the three series: in the first series it is the methyl- and methoxy-substitution that has a positive effect, though limited to the diethylacetyl-derivatives **7** and **9**; in the other two series it is the trifluoromethyl substitution that exerts this effect in the case of the dimethylacetyl-derivatives **13** and **22**, while in the case of the diethylacetyl-derivatives it is limited to the nitro-compound **25**.

As for the influence of the two chemico-physical parameters under consideration, the following observations can be made: in the series of nitroderivatives the two active compounds **22** and **25** have the lowest pka and the highest log P of their respective series (dimethyl- and diethylacetyl-derivatives), and it can therefore be assumed that the active species of these substances is the ionised form, its enhanced lipophilia facilitating its subsequent migration across the haematoencephalic barrier.

In the 2-aminobenzenesulfon-N-acylamide series, too, the active compound **13** is that with the lowest pka and the highest log P of its series (dimethylacetyl-derivatives);

furthermore, its corresponding higher homologue **17**, which has a pka value comparable to that of **13**, but greater lipophilia, is practically inactive.

In the 2-acylamino-derivative series a high log P value does not have a favourable effect either, and the two active compounds **7** and **9** have fairly similar log P values (2.13 and 2.01, resp.) that are midway between the lowest (1.62 for **6**) and the highest (2.55 and 3.06 for **10** and **8**, resp.) recorded for the other compounds of the series to which they belong. If the pka and log P values of **7** and **9** are then compared with their lower homologues **2** and **4**, both of which are inactive, it can be seen that the latter compounds' pka values are higher (albeit slightly) and their log P values markedly lower than those recorded for their corresponding active homologues.

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# Herstellung und Eigenschaften von β-Ketopropansultonen und -sultamen

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Durch *Dieckmann*-Kondensation wurden die 1,2-Oxathiolan-4-on-2,2-dioxide **5** und Isothiazolidin-4-on-1,1-dioxide **6** hergestellt. Alle Verbindungen besitzen $pK_s$-Werte um 4. Bemerkenswert ist die große Alkalistabilität insbesondere der Sultone **5**.

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