

Note

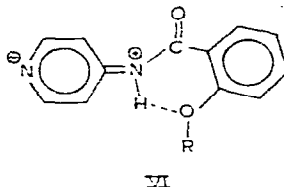
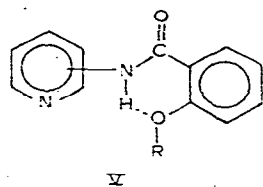
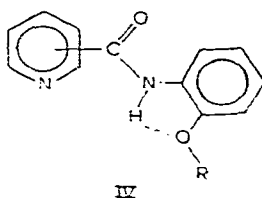
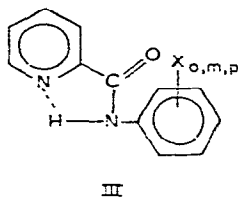
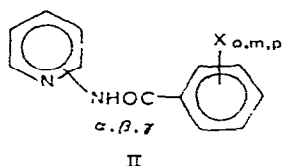
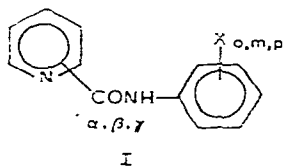
**Thin-layer chromatography of anilides of pyridinecarboxylic acids and benzamidopyridines**

J. MIREK and J. DYDUŁA

*Institute of Chemistry of the Jagiellonian University, ul. Krupnicza 41, 30-060 Krakow (Poland)*

(First received January 9th, 1978; revised manuscript received October 23rd, 1978)

It is well established that some properties, for example solubility in non-polar solvents, of compounds that have at least two polar sites in the molecule, such as anilides of pyridinecarboxylic acids, depend not only on the chemical structure and substituents present, but also on the molecular structure resulting from the hydrogen bonding<sup>1,2</sup>. Possible inter- and intramolecular hydrogen bonding<sup>3-6</sup> in compounds with structures I and II may cause greater differences than any other factor during their thin-layer chromatography (TLC).



It seemed worth investigating whether there are any regularities between the  $R_F$  and  $R_M$  values of compounds I and II, and whether they could be applied in the TLC of the other series of anilides of heterocyclic carboxylic acids.

## EXPERIMENTAL

The compounds investigated were obtained by methods described elsewhere<sup>2,7</sup>.

Of the many solvent mixtures tested, benzene-chloroform-acetone (1:1:1) and 0.5–0.7% concentrations of the investigated compounds appeared to be the most suitable conditions for our purpose, giving the best separations with sharp, symmetrical spots (developed with iodine) localized between  $R_F = 0.15$  and 0.8.

In preliminary experiments, silica gel and aluminium oxide gave similar results. Merck silica gel 60 pre-coated TLC plates (20 × 20 cm) were used in the final measurements.

Prior to use, the plates were dried for 30 min at 105° and then cooled in a desiccator over anhydrous calcium chloride.

Small drops (0.005–0.007 cm<sup>3</sup>) of solution were placed 2.5 cm from the lower edge of the plate, starting 2 cm from the side and 1 cm apart. In one set three plates were dipped 4 mm into the mixture of solvents in a glass box of dimensions 20.8 × 12.8 × 21.8 cm and having one wall lined with filter-paper. The silica gel-coated side of each plate was placed facing the unlined wall of the box, which was then tightly covered.

## RESULTS AND DISCUSSION

The results (Table I) showed a stronger influence of the secondary structural properties of the compounds investigated (for example, nature of hydrogen bonding) on the rates of their migration during TLC than the presence of even moderately polar substituents.

The position of the carboxamido group ( $\alpha$ -,  $\beta$ - or  $\gamma$ -) in anilides of pyridine-carboxylic acids appeared crucial for their separation by TLC. This effect occurred to a lesser extent with isomeric benzamidopyridines ( $\alpha$ -,  $\beta$ - or  $\gamma$ -).

*Compounds with structure I*

Transfer of the carboxamido group (CONH) from the  $\alpha$ - to the  $\beta$ -position changed the  $R_M$  value by 0.75 and from the  $\beta$ - to the  $\gamma$ -position by only 0.075. This large difference in  $R_M$  and the direction of its change may be caused, apart from other less important factors, by strong intramolecular hydrogen bonding in all anilides of  $\alpha$ -pyridinecarboxylic acid (III). The intramolecular hydrogen bonding opposes the intermolecular association of the compound being chromatographed. This effect lowers the adsorption of the compounds being chromatographed on the adsorbent and thus facilitates their migration in comparison with other anilides, especially with those prone to associate by intermolecular hydrogen bonding.

With methyl, chlorine and bromine substituents the  $R_M$  value changes by only 0.06 on changing the *ortho* position in the aniline moiety to *meta* or *para*.

An ethoxy substituent gave a slightly more complicated but still clear influence. On changing the *ortho* position to *meta* caused, the change in  $\Delta R_M$  was 0.025 for the  $\alpha$ -isomer (Table I, 13 → 16) and 0.303 and 0.277 for the  $\beta$ - and  $\gamma$ -isomers (16 → 17 and 19 → 20), respectively.

Smaller differences in  $R_M$  were observed when the position of an ethoxyl substituent was changed from *meta* to *para*, the values being 0.039, 0.082 and 0.090

TABLE I  
THIN-LAYER CHROMATOGRAPHY OF ANILIDES OF PYRIDINECARBOXYLIC ACIDS  
AND BENZAMIDOPYRIDINES AT 22-23°

No.	Compound	$R_F \times 100^*$	$R_M^{**}$
1	I $\alpha$	66	-0.2938
2	I $\beta$	27	0.4401
3	I $\gamma$	23	0.5225
4	I $\alpha$ - <i>o</i> -CH <sub>3</sub>	68	-0.3309
5	I $\alpha$ - <i>m</i> -CH <sub>3</sub>	68	-0.3239
6	I $\beta$ - <i>o</i> -CH <sub>3</sub>	28	0.4194
7	I $\gamma$ - <i>o</i> -CH <sub>3</sub>	26	0.4595
8	I $\gamma$ - <i>p</i> -CH <sub>3</sub>	23	0.5170
9	I $\alpha$ - <i>p</i> -OCH <sub>3</sub>	64	-0.2448
10	I $\beta$ - <i>o</i> -OCH <sub>3</sub>	36	0.2504
11	I $\beta$ - <i>p</i> -OCH <sub>3</sub>	24	0.5095
12	I $\gamma$ - <i>o</i> -OCH <sub>3</sub>	31	0.3439
13	I $\alpha$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	70	-0.3705
14	I $\alpha$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	69	-0.3454
15	I $\alpha$ - <i>p</i> -OC <sub>2</sub> H <sub>5</sub>	67	-0.3062
16	I $\beta$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	44	0.1123
17	I $\beta$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	28	0.4177
18	I $\beta$ - <i>p</i> -OC <sub>2</sub> H <sub>5</sub>	24	0.4999
19	I $\gamma$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	39	0.2026
20	I $\gamma$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	25	0.4801
21	I $\gamma$ - <i>p</i> -OC <sub>2</sub> H <sub>5</sub>	21	0.5710
22	I $\alpha$ - <i>p</i> -Cl	66	-0.2895
23	I $\beta$ - <i>p</i> -Cl	26	0.4618
24	I $\gamma$ - <i>p</i> -Cl	23	0.5126
25	I $\alpha$ - <i>p</i> -Br	67	-0.3051
26	I $\beta$ - <i>p</i> -Br	25	0.4695
27	I $\gamma$ - <i>p</i> -Br	23	0.5864
28	II $\alpha$	59	-0.1612
29	II $\beta$	26	0.4582
30	II $\gamma$	17	0.6794
31	II $\alpha$ - <i>p</i> -CH <sub>3</sub>	61	-0.1973
32	II $\gamma$ - <i>p</i> -CH <sub>3</sub>	19	0.6213
33	II $\alpha$ - <i>p</i> -OCH <sub>3</sub>	56	-0.0989
34	II $\beta$ - <i>p</i> -OCH <sub>3</sub>	22	0.5403
35	II $\gamma$ - <i>p</i> -OCH <sub>3</sub>	16	0.7192
36	II $\alpha$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	67	-0.3003
37	II $\alpha$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	64	-0.2512
39	II $\beta$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	61	-0.1979
40	II $\beta$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	32	0.3348
41	II $\beta$ - <i>p</i> -OC <sub>2</sub> H <sub>5</sub>	27	0.4370
42	II $\gamma$ - <i>o</i> -OC <sub>2</sub> H <sub>5</sub>	25	0.4695
43	II $\gamma$ - <i>m</i> -OC <sub>2</sub> H <sub>5</sub>	23	0.5149
44	II $\gamma$ - <i>p</i> -OC <sub>2</sub> H <sub>5</sub>	18	0.6464
45	II $\alpha$ - <i>p</i> -Cl	62	-0.2172
46	II $\beta$ - <i>p</i> -Cl	27	0.4242
47	II $\gamma$ - <i>p</i> -Cl	18	0.6556
48	II $\alpha$ - <i>p</i> -Br	63	-0.2232
49	II $\beta$ - <i>p</i> -Br	18	0.5656

\* Solvent: benzene-chloroform-acetone (1:1:1), developed three times.

\*\*  $R_M = (1/R_F) - 1$ .

for the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers, respectively. Incomplete data for the methoxyl group showed a similar influence; for example, the change in  $R_M$  was 0.250 when the methoxyl group was shifted from *ortho* to *para* (10  $\rightarrow$  11).  $\alpha$ -Alkoxy and -amide groups can form intramolecular hydrogen bonds (IV), but they will be weaker than those in compounds with structure III because of the unfavourable difference in the basicity of the ether oxygen atom in comparison with the pyridine nitrogen atom. As a result of this fact, the adsorptivity of such compounds decreases slightly but its migration rate does not change very much.

#### Compounds with structure II

The change in  $R_M$  on going from  $\alpha$ - to  $\beta$ -isomers is only three times as great as that on going from  $\beta$ - to  $\gamma$ -isomers (lack of intramolecular hydrogen bonding).

TLC did not give any conclusive information about the interaction of amide groups (NH) with ethoxy oxygen for  $\alpha$ -isomers. With  $\beta$ -isomers, the observed four-fold greater difference in  $R_M$  on going from the *ortho* to the *meta* isomer over that on going from the *meta* to the *para* isomer suggest weak intramolecular hydrogen bonding (V).

The inconsistency between TLC data (Table I) and IR data<sup>3</sup> for compound 42 is the sole deviation from the rule that intramolecular hydrogen bonding increases the rate of migration of a compound in chromatography. The unexpected slower migration of compound 42 in TLC may be connected with an enhanced basicity of the pyridine nitrogen atom (VI) owing to the participation of a polar structure<sup>8</sup> which caused a stronger interaction of that compound with the adsorbent.

#### REFERENCES

- 1 G. C. Pimentel and A. C. McClellan, *The Hydrogen Bond*, Freeman, San Francisco, 1960.
- 2 J. Mirek, *Rocz. Chem.*, 40 (1966) 205.
- 3 J. Mirek and J. Paško, *Rocz. Chem.*, 41 (1967) 2083.
- 4 J. Mirek and B. Kawalek, *Tetrahedron*, 26 (1970) 1261.
- 5 L. R. Snyder, *Principles of Adsorption Chromatography*, Marcel Dekker, New York, 1968.
- 6 M. Palamareva and B. J. Kurtev, *J. Chromatogr.*, 132 (1977) 61.
- 7 H. Rinderknecht, *Helv. Chim. Acta*, 42 (1959) 1324.
- 8 M. Brenner and G. Pataki, *Helv. Chim. Acta*, 44 (1961) 1420.