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GAS CHROMATOGRAPHY OF SOME NITROGEN AND SULFUR HETEROCYCLES BY MEANS OF SILICONE AND BENTONE–SILICONE PHASES

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SUMMARY

Gas chromatographic retention ratios are reported for 49 compounds in the thiophene, benzo(*b*)thiophene, pyridine, quinoline, isoquinoline, and thienopyridine ring systems, variously substituted with alkyl and halo groups. Stationary phases of Silicone DC 710 and of Bentone 34–Silicone DC 710 on Chromosorb were used at 128° and 180°. Retention ratio data for silicone are interpreted in terms of volatility of the substrate. Changes in retention ratios on going to Bentone–silicone are ascribed to adsorption to Lewis acidic sites (on the Bentone aluminosilicate sheets) by coordination of the heterocyclic nitrogen atom of the substrate molecule, particularly in the pyridine, quinoline, and thieno(2,3-*b*)pyridine systems (studied most extensively).

INTRODUCTION

Recent synthetic studies in these laboratories have been concerned with thienopyridines and their derivatives[1–5]. Interest in examination of their physical properties and means of separation led us to compare the chromatographic retentivities of these compounds with those of analogous heterocyclic amines in thin-layer systems[6]. We have now extended these studies to comparison of gas chromatographic (GC) retention ratios, R, for parent, alkyl-substituted, and halo-substituted compounds in the thiophene, benzo(*b*)thiophene, pyridine, quinoline, isoquinoline, and thienopyridine systems. Selected as stationary phases were Silicone DC 710 on Chromosorb and Bentone 34-Silicone DC 710 on Chromosorb[7]. Modified Bentone columns have been found to be useful in effecting separations of isomeric aromatic hydrocarbons[7–13]. However, it seems that no previous use of such columns for gas chromatography of amines has been reported. In order to elucidate the nature of interactions between the substrate molecules and Bentone 34, retention ratios *versus* the same standard of reference,

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benzo(*b*)thiophene, were compared for each substrate on the two columns (under otherwise closely similar conditions). Compounds investigated are listed in Tables I–III.

EXPERIMENTAL

Starting materials

Unless otherwise stated, all compounds used were commercially available samples. 4,8-Dimethylquinoline[14] and thieno(3,2-*c*)pyridine[15] were synthesized by reported methods. Other thienopyridine compounds were available from research conducted in our laboratory[1–5].

Chromatographic procedure

The apparatus used was an F and M Model 810 dual column analytical gas chromatograph with a thermal conductivity detecting system and a Leeds and Northrup 10-mV electronic recorder. Stationary phase *S* was 10 % Silicone Fluid DC 710 on 60–80 mesh Chromosorb G, packed in copper tubing 3/8 in. (O.D.) × 6.26 ft. Stationary phase *BS* was 5 % Bentone 34 plus 5 % Silicone Fluid DC 710 on 60–80 mesh Chromosorbs G and W (4:5, by wt.), packed in copper tubing 3/8 in. × 5.26 ft.

TABLE I

VPC RETENTION RATIOS (*R*) OF THIOPHENE AND PYRIDINE COMPOUNDS AT 128°

No.	*Compound*	*B.p.*[a] (°C)	R_S[b]	R_{BS}[c]	R_{BS}/R_S
1	Benzo(*b*)thiophene[d]	221.5	1.00[e]	1.00[f]	1.0
2	2-Me-thiophene	113	0.10	0.09	0.9
3	3-Me-thiophene	115.4[g]	0.10	0.08	0.8
4	2-Cl-thiophene	128.3	0.14	0.23	1.6
5	Pyridine	115.3	0.08	0.07	0.9
6	2-Me-pyridine	129.4	0.15	0.07	0.5
7	3-Me-pyridine	144.1	0.14	0.11	0.8
8	4-Me-pyridine	145.4	0.16	0.13	0.8
9	2,4-DiMe-pyridine	158.4	0.21	0.16	0.8
10	3,4-DiMe-pyridine	178.8[h,i]	0.34	0.27	0.8
11	3,5-DiMe-pyridine	171.9	0.30	0.24	0.8
12	2-Et-pyridine	148.5	0.19	0.11	0.6
13	4-Et-pyridine	169.8[j]	0.27	0.21	0.8
14	2,4,6-TriMe-pyridine	176.5	0.30	0.19	0.6
15	2-Cl-pyridine	170	0.24	0.53	2.2
16	2,5-DiCl-pyridine	190.5[h]	0.46	0.70	1.5
17	2,6-DiCl-pyridine	211.5[h]	0.60	1.37	2.3
18	3,5-DiCl-pyridine	178.5[h]	0.34	0.42	1.2

[a] Unless noted otherwise, data are taken from ref. 17.
[b] $R_S = R$ for 10% silicone column, phase *S*.
[c] $R_{BS} = R$ for 5% Bentone–5% silicone column, phase *BS*.
[d] Internal standard in all runs.
[e] Corresponds to a retention time of 10–15 min.
[f] Corresponds to a retention time of 20–30 min.
[g] From ref. 18.
[h] From ref. 19.
[i] Ref. 17 gives a low value of 164°.
[j] At 750 mm.

TABLE II

VPC RETENTION RATIOS (R) OF QUINOLINES AND ISOQUINOLINES AT 180°

No.	*Compound*	*B.p.*[a] (°C)	R_S[b]	R_{BS}[c]	R_{BS}/R_S
1	Benzo(*b*)thiophene[d]	221.5	1.00[e]	1.00[f]	1.0
19	Quinoline	238	1.19	1.93	1.6
20	Isoquinoline	242	1.32	1.75	1.3
21	2-Me-quinoline	247.6	1.62	1.95	1.2
22	4-Me-quinoline	262	2.17	3.77	1.7
23	5-Me-quinoline	254[g]	1.86	3.52	1.9
24	7-Me-quinoline	252	1.86	2.97	1.6
25	8-Me-quinoline	247.8[h]	1.66	2.14	1.3
26	3-Br-quinoline	275	3.31	4.19	1.3
27	1-Me-isoquinoline	248	1.89	2.50	1.3
28	2,4-DiMe-quinoline	264.5	2.72	4.75	1.7
29	2,6-DiMe-quinoline	266.5	2.44	3.47	1.4
30	2,8-DiMe-quinoline	252	2.02	2.13	1.1
31	4,6-DiMe-quinoline	273.5	3.35	7.33	2.2
32	4,8-DiMe-quinoline	258.5	2.77	3.36	1.2
33	2-Cl-4-Me-quinoline	296	4.45	11.5	2.6

[a–d] See corresponding footnote in Table I.
[e] Corresponds to a retention time of 3–4 min.
[f] Corresponds to a retention time of *ca.* 5 min.
[g] At 735 mm.
[h] At 751 mm.

Before use, columns were conditioned at 200° for 24 h with a gentle flow of helium gas. Experiments were conducted at column temperatures of 128° (helium flow rate, 170 ml/min) for monocyclic compounds (Table I) and at 180° (helium flow rate, 225 ml/min) for bicyclic compounds (Tables II and III). Samples (10–20 μl) of solutions containing 25 mg of substrate plus 25 mg of benzo(*b*)thiophene (internal reference standard) per ml of solvent (benzene or acetone) were injected into the chromatograph. Adjusted retention times were measured in linear units from the air peak. In each run the adjusted retention time for the substrate was divided by that for the standard to give the relative adjusted retention ratio[16], designated here simply as "retention ratio". Average retention ratios (R_S for phase S, R_{BS} for phase BS) for duplicative runs (maximum variation in R, $\pm 5\%$) are given in Tables I–III.

RESULTS AND DISCUSSION

Observation of Tables I and II shows that there is a general increase in retention ratio with increasing normal boiling point (*i.e.* with decreasing volatility) in these simple derivatives of pyridine, thiophene, and their benzo analogs with silicone oil as the stationary phase. This approximate relationship is presented in Figs. 1 and 2, where log R_S is plotted *vs.* the temperature of the normal boiling point[20].

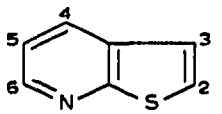
Boiling points of the thienopyridines in Table III have not been determined. However, one finds very close values of R_S for the thienopyridine isosteres[21,22] (*cf.* Nos. 34, 35; 36, 37) in Table III. Moreover, these values are 8–10 % higher than for their respective isosteres, quinoline and isoquinoline (Nos. 19; 20), in Table II. Also, derivatives of thieno(2,3-*b*)pyridine have R_S values *ca.* 5 % higher than do their iso-

TABLE III

VPC RETENTION RATIOS (R) OF THIENOPYRIDINES AT 180°

No.	*Compound*	R_S[a]	R_{BS}[b]	R_{BS}/R_S
1	Benzo(*b*)thiophene[c]	1.00[d]	1.00[e]	1.0
34	Thieno(2,3-*b*)pyridine[f]	1.30	2.86	2.2
35	Thieno(3,2-*b*)pyridine[f]	1.29	1.84	1.4
36	Thieno(2,3-*c*)pyridine[f]	1.45	2.73	1.9
37	Thieno(3,2-*c*)pyridine[f]	1.43	2.12	1.5
38[g]	4-Me-thieno(2,3-*b*)pyridine	2.26	5.23	2.3
39	6-Me-thieno(2,3-*b*)pyridine	1.70	2.97	1.7
40	4-Et-thieno(2,3-*b*)pyridine[h]	3.24	7.70	2.4
41	6-Et-thieno(2,3-*b*)pyridine[h]	2.48	3.57	1.4
42	4,6-DiMe-thieno(2,3-*b*)pyridine	2.86	6.70	2.3
43	4,5,6-TriMe-thieno(2,3-*b*)pyridine	6.05	11.0	1.8
44	3-Br-thieno(2,3-*b*)pyridine[h]	3.31	4.48	1.4
45	5-Cl-thieno(2,3-*b*)pyridine	2.46	4.68	1.9
46	5-Br-thieno(2,3-*b*)pyridine	3.49	5.37	1.5
47	2,3-DiCl-thieno(2,3-*b*)-pyridine[h]	3.64	5.08	1.4
48	6-Et-thieno(3,2-*b*)pyridine[i]	3.09	3.55	1.2
49	6-Me-thieno(3,2-*c*)pyridine[j]	1.81	2.24	1.2

[a–c] See footnotes b–d, respectively, in Table I.
[d, e] See footnotes e and f, respectively, in Table II.
[f] Structural formulas:



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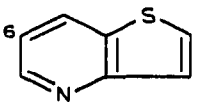

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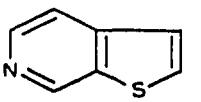

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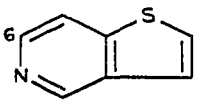

No. 37

[g] For Nos. 38 to 47, see formula 34.
[h] Data on the syntheses and structures of these compounds will be reported elsewhere.
[i] See formula 35.
[j] See formula 37.

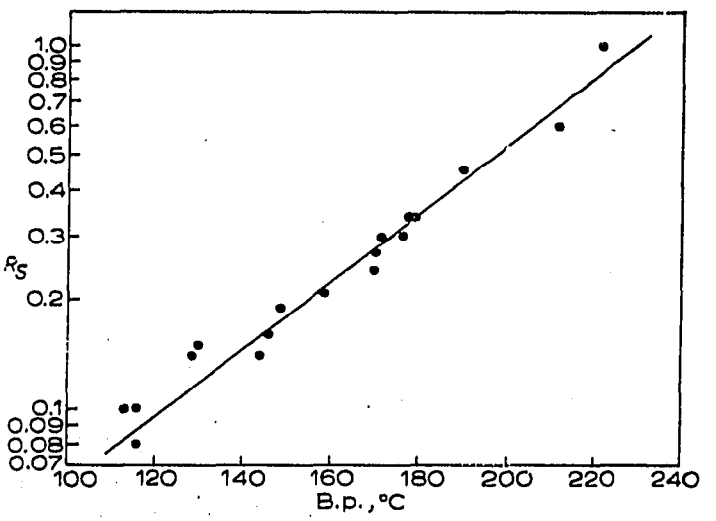

Fig. 1. Plot of log R_S *vs.* temperature of normal boiling point for compounds in Table I.

steric substituted quinolines (*cf.* 21, 39; 22, 38; 26, 46; 28, 42). It is, therefore, reasonable to assume that special polar or steric interactions do not occur between stationary phase *S* and the thienopyridine substrates studied. Hence, Fig. 2 and the R_S values in Table III might well serve as a means of estimating normal boiling points for compounds 34–49.

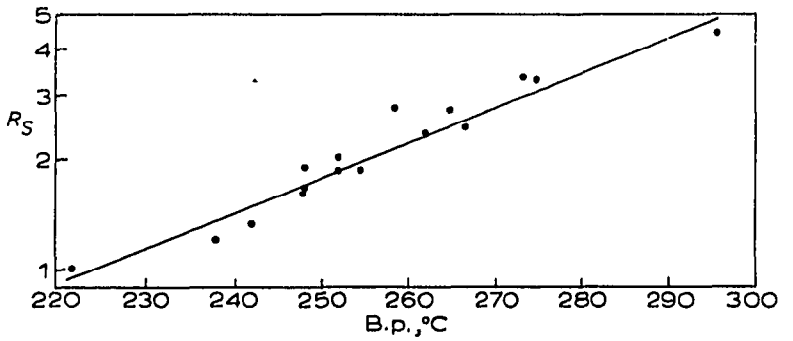

Fig. 2. Plot of log R_S *vs.* temperature of normal boiling point for compounds in Table II.

In general, retention times were larger for every compound with the *BS* phase than the *S* phase, despite the shorter column used in the former case. (See footnotes e and f in Tables I and II). The ratio $R_{BS}/R_S = r$ is taken as a simple criterion for evaluation of structural features pertinent to retention of substrates on Bentone *per se*. In this regard one notes that for all monocyclic compounds studied which have 0–3 alkyl groups (Nos. 2, 3, 5–14) $r < 1.0$. For all halogen-bearing monocyclic compounds and all bicyclic compounds, on the other hand, $r \geq 1.0$. For only eight substrates is $r > 2.0$. Three of these eight (Nos. 15, 17, 33) have at least one chlorine atom α to nitrogen and four (Nos. 34, 38, 40, 42) are thieno(2,3-*b*)pyridines (sulfur atom α to nitrogen). In fact for each of the 15 compounds studied which has either a chlorine or a sulfur atom α to nitrogen $r \geq 1.4$ and averages 1.9, as compared to an average of 1.5 for all other 21 substrates for which $r > 1.0$. For 2-chlorothiophene (chlorine atom α to sulfur) $r = 1.6$.

For interpretation of these r values it is instructive to consider briefly the known structure of the stationary *BS* phase. Bentone 34 (dimethyldi-*n*-octadecylammonium montmorillonite)[7] is a non-stoichiometric (but electrically neutral) compound containing aluminosilicate sheets intercalated with tetraalkylammonium ions, $(CH_3)_2N^+R_2$, where $R = (CH_2)_{17}CH_3$[23–25]. Net negative electronic charge on the sheets results from isomorphous replacements of Al(III) and Si(IV) atoms with metallic elements of lower valence. The interfacial surfaces of the sheets bear incompletely coordinated metal atoms, M^{n+} (where M = Si or Al), which may serve as Lewis acidic sites. As determined by X-ray measurements, the interlayer distance is more than 18 Å. In accordance with proposals for monoalkylammonium montmorillonites[26], it is presumed that the positive centers of the intercalated ions lie close to the interfacial surfaces, while the long R groups from a relatively thick interlamellar non-polar region, also occupied by molecules of silicone in Bentone–silicone mixtures. Our substrate molecules are sufficiently small in size that they should readily penetrate into the non-polar region. The marked retention of polar molecules by montmorillonites[27] is ascribed to adsorption at the interfacial surfaces, where aspects of size, shape, and orientation of the substrate molecule become pertinent.

The high r values for the α-chloropyridines, the α-chloroquinoline (No. 33), and the thieno(2,3-*b*)pyridines (Nos. 34, 38–47) are consistent with retention of these molecules by Bentone 34 by means of simultaneous coordination (chelation) of both the ring nitrogen atom and its α-nucleophilic substituent atom (X) to a single Lewis acidic site on the aluminosilicate sheet (see Fig. 3). A similar chelate structure could

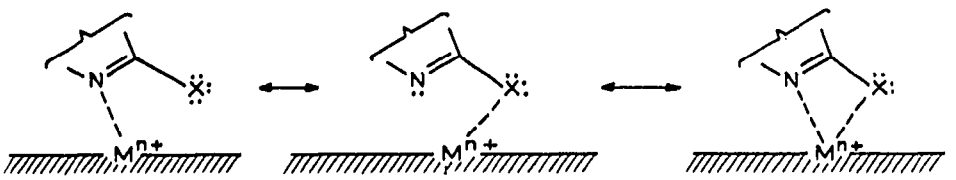

Fig. 3.

be formed with 2-chlorothiophene. The marked difference in R_{BS} values for thieno(2,3-*b*)- and thieno(3,2-*b*)pyridines is especially notable. The general phenomenon of simultaneous anchoring by two favorably juxtaposed sites on the adsorbate to one site on the adsorbent is a familiar one in chromatography[6,28].

Steric hindrance by an alkyl group α to the heterocyclic nitrogen atom is readily apparent in the chelated thieno(2,3-*b*)pyridine system. Thus, contributions toward the r value fall in the orders γ-Me > H > α-Me (Nos. 34, 38, 39); γ-Et > H > α-Et (Nos. 34, 40, 41); α-Me > α-Et; and α,γ-diMe > α,β,γ-triMe (Nos. 42, 43 — buttressing effect). Steric hindrance to coordination at the nitrogen atom is also noted in compounds where chelation is impossible. One finds orders (in r) of γ-Me = β-Me > α-Me (Nos. 6–8), γ-Et > α-Et (Nos. 12, 13), and α, γ-diMe > α,α', γ-triMe (Nos. 9, 14) in the pyridine system as well as 5-Me, 7-Me, γ-Me ≥ H > *peri*-Me > α-Me (Nos. 19, 21–25) and γ,6-diMe > α,γ-diMe > H > α,6-diMe > γ,*peri*-diMe > α,*peri*-diMe (Nos. 19, 28–32) in the quinoline system and H > α-Me (Nos. 37, 49) in the thieno(3,2-*c*)pyridine system.

For 3-bromoquinoline (No. 26) and the halo-substituted thieno(2,3-*b*)pyridines (Nos. 44–47) wherein the halogen atom occupies a position removed from the nitrogen atom, the halo derivative has an r value lower than that of its parent compound. This is consistent with electron withdrawal from the nitrogen atom by the halogen atom. The order 5-chlorothieno(2,3-*b*)pyridine > 5-bromothieno(2,3-*b*)pyridine (*cf.* Nos. 45, 46) may reflect differences in bulkiness of the halogen atoms, in addition to differences in their electron withdrawing abilities. It might be noted, however, that 3,5-dichloropyridine (No. 18) does not fit this model well.

On the basis of the foregoing relationships it seems fairly clear that, in general, the pyridinoid ring in our compounds is adsorbed by coordination through the n-electrons of the nitrogen atom to a Lewis acidic site on the aluminosilicate sheet in the Bentone–silicone phase. Since only oxygen atoms are believed to occupy the outermost layer of each face of this sheet while the acidic sites occupy the second layer (partially exposed), it seems probable that the coordinated pyridinoid ring will assume a perpendicular or tilted geometry with respect to the plane of the sheet[29]. Effects of steric hindrance by alkyl groups α to the nitrogen atom would be most pronounced in such an orientation.

Insufficient data are presented for the thiophene, isoquinoline, and two thienopyridine systems (Nos. 35, 36) to permit meaningful interpretations to be made in these cases.

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