Journal of Chromatography, 537 (1991) 371–376
Elsevier Science Publishers B.V., Amsterdam

CHROM. 22 773

Correlation between structure and gas chromatographic behaviour of nitrogen-containing heterocyclic compounds

II. Alkyl substitution of quinazolone derivatives

O. PAPP, Gy. SZÁSZ* and L. ŐRFI
Institute of Pharmaceutical Chemistry, Semmelweis Medical University, Hőgyes E. ú. 9, H-1092 Budapest (Hungary)
and
I. HERMECZ
Chinoin Pharmaceutical Works, Budapest (Hungary)
(First received March 29th, 1990; revised manuscript received August 21st, 1990)

ABSTRACT

Mono- and dialkyl-substituted quinazolones were synthesized by literature or its modifications. Six homologous series were prepared, varying in the substituent introduced and its position. The retention indices of the compounds were determined on OV-1 and OV-25 stationary phases. The influence of the number of carbon atoms in the homologues alkyl chain on the *I* and *AI* values could be characterized well. The behaviour of the alkylquinazolones and the ring-closed tricyclic with the same number of carbon atoms could also be characterized numerically. A dominant effect was exerted by the substituent in the neighbouring position to the alkyl chain.

INTRODUCTION

2,3-Substituted quinazolone derivatives include many compounds with valuable pharmacological effects [1], *e.g.*, a theophylline-like antiasthmatic effect [2,3]. The bronchodilator effect varies considerably as a function of the substitution. It is maximum for the condensed ring and the corresponding disubstitution [4]. During an analysis of the physico-chemical parameters of pyrido[1,2-*a*]pyrimidines and quinazolones with an antiasthmatic effect, we characterized the structural features connected with the action of many nitrogen-containing tricyclics [5,6]. This paper describes a gas chromatographic investigation and the quantitative relationship between the structure and phisico-chemical properties of 2,3-substituted quinazolones.

EXPERIMENTAL

The apparatus and chromatographic conditions were as described in Part I [7].

0021-9673/91/$03.50

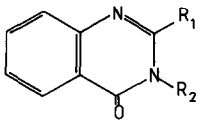
The 2,3-substituted quinazolones were synthesized by appropriate modification of the original literature methods [8].

RESULTS AND DISCUSSION

Six homologous series of alkyl-substituted 4-oxoquinazoline derivatives were prepared with various substituents R_1 and R_2 (Table I). The homologous series

TABLE I

SERIES OF COMPOUNDS AND RETENTION INDEX VALUES



No. of series	R_1	R_2	$I^{OV\text{-}1}_{220°C}$	$I^{OV\text{-}25}_{220°C}$	ΔI
1	H	H	1733	2360	627
	CH_3	H	1736	2337	601
	C_2H_5	H	1788	2365	577
	C_3H_7	H	1853	2418	565
	C_4H_9	H	1955	2509	554
	C_5H_{11}	H	2050	2604	554
2	CH_3	CH_3	1733	2293	560
	C_2H_5	CH_3	1800	2333	533
	C_3H_7	CH_3	1865	2380	515
	C_4H_9	CH_3	1957	2467	510
	C_5H_{11}	CH_3	2050	2551	501
3	CH_3	C_2H_5	1749	2276	527
	C_2H_5	C_2H_5	1805	2302	497
	C_3H_7	C_2H_5	1869	2349	480
	C_4H_9	C_2H_5	1962	2430	468
	C_5H_{11}	C_2H_5	2050	2515	465
4	H	H	1733	2360	627
	H	CH_3	1639	2201	562
	H	C_2H_5	1664	2199	535
	H	C_3H_7	1740	2265	525
	H	C_4H_9	1835	2349	514
	H	C_5H_{11}	1926	2442	516
5	CH_3	H	1736	2337	601
	CH_3	CH_3	1733	2293	560
	CH_3	C_2H_5	1749	2276	527
	CH_3	C_3H_7	1826	2330	504
	CH_3	C_4H_9	1915	2416	501
	CH_3	C_5H_{11}	2003	2507	504
6	C_2H_5	H	1788	2365	577
	C_2H_5	CH_3	1800	2333	533
	C_2H_5	C_2H_5	1805	2302	497
	C_2H_5	C_3H_7	1873	2350	477
	C_2H_5	C_4H_9	1961	2430	469
	C_2H_5	C_5H_{11}	2050	2520	470

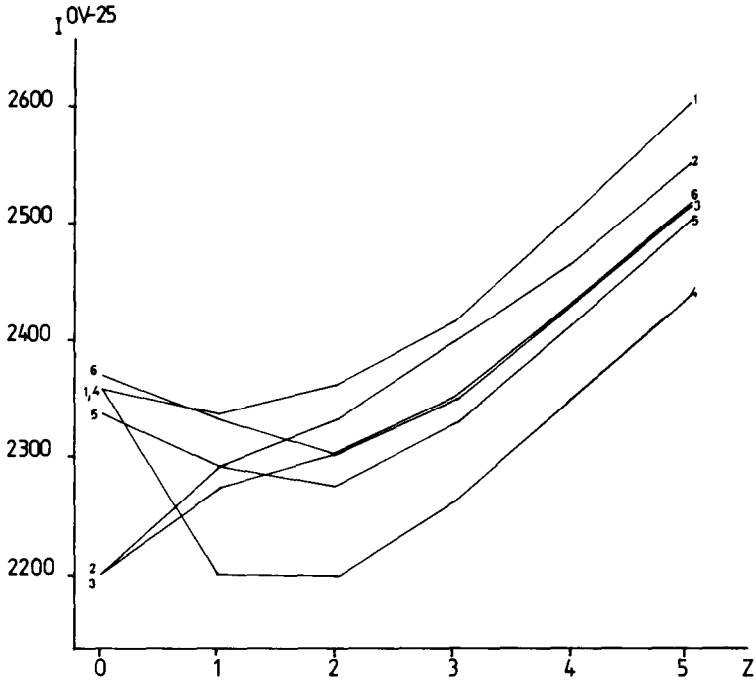


Fig. 1. Relationship between number of carbon atoms (z) and retention index of compounds in homologous series. Series 1–6 as in Table I.

contain C_1–C_5 substituents with the differences that the homologous series are connected to C-2 or N-3 with hydrogen, methyl or ethyl on the other atom. The retention index values measured on stationary phase OV-1 are represented as a function of the number of carbon atoms in Fig. 1. The initial parts of the curves verify the relationship formulated by Kováts: for an alkyl group connected to a polar functional group, $dI^{apol}_{(CH_2)_{z+1}} - dI^{apol}_{(CH_2)_z} \approx 100$ index units (i.u.) only if $z > 5$.

The different courses of the six curves also demonstrate that the retention index and dI_{CH_2} increment values obtained do not depend only on whether the alkyl chain is connected to C-2 or N-3; their values are additionally influenced by the constant sibstituents of the individual series (H, CH_3, C_2H_5). The influence of the R_1 and R_2 substituents on the retention properties of the molecule can be studied better if the ΔI values are depicted as a function of the number of carbon atoms (Fig. 2). The resulting exponential curves are described by the equation

$$\Delta I = a \cdot 10^{-bz} + c$$

where a, b and c are empirical constants and z is the number of carbon atoms. The values of the constants were determined by the method of least squares by iteration. The optimum values were indicated by the correlation coefficient. The mean of the difference between the measured and calculated values was less than 1.5 i.u. The

graphical representation reveals that for the different disubstituted derivatives the polarity curves of the homologous series follow almost the same course, which means that an increase in the length of the alkyl groups at positions 2 and 3 of the quinazolone skeleton causes essentially the same change in polarity. There is an important difference in the retention behaviour of the two monosubstituted series. This difference can be attributed to the free NH group, which can interact specifically with the polar stationary phase and may form a hydrogen bridge.

From a comparison of the two series, the extent of this interaction can be expressed numerically for the given pair of stationary phases as 39 $\pm$ 2 i.u. The extent of the change in polarity can be followed better via the derivatives of the polarity curves. Differentiation of eqn. 1 with respect to z gives

$$\frac{d\Delta I}{dz} = ab \cdot \ln 10 \cdot 10^{-bz} \tag{2}$$

which expresses the polarity change per carbon atom change. By representing the results for the six series graphically, we obtain the curves shown in Fig. 3.

The changes in the degree of polarity in the four homologous series with alkyl disubstitution are nearly the same; they decrease exponentially with an increase in the number of carbon atoms, and for $z > 5$ tend to zero. The 2-alkylquinazolone homologues display the smallest decrease in polarity and the 3-alkylquinazolones the steepest. On the above basis it appars that the relationship between the number of carbon atoms for $z = 0$–5 and the ΔI values representing the polairty of the compound can be applied generally for homologous series containing a polar functional group.

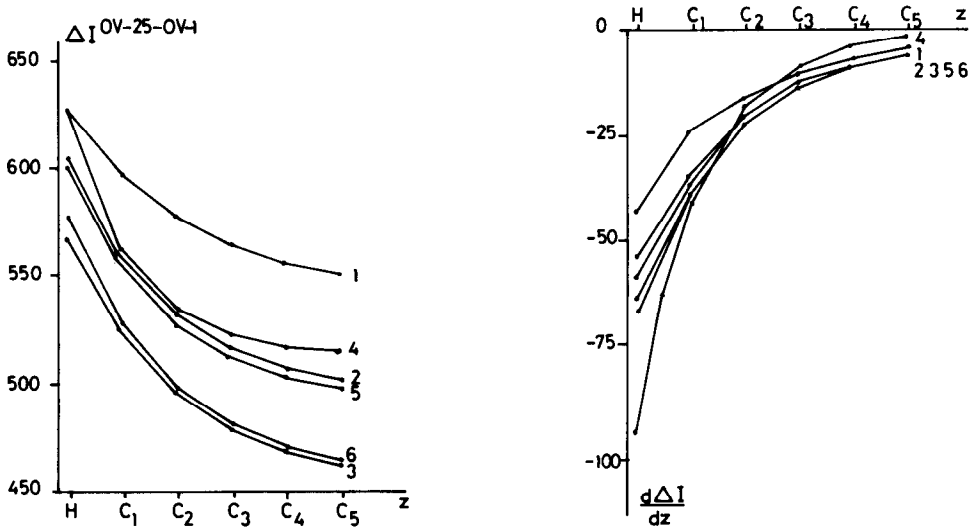
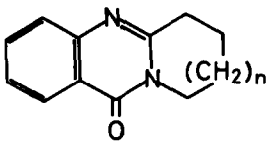


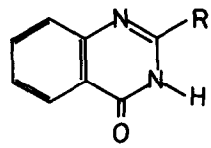
Fig. 2. Relationship between number of carbon atoms (z) and polarity of compounds in homologous series. Series 1–6 as in Table I.

Fig. 3. Derived curves of correlation between number of carbon atoms and polarity.

TABLE II

DIFFERENCE IN POLARITY OF NITROGEN-CONTAINING TRICYCLIC AND ALKYL-SUBSTITUTED QUINAZOLONES WITH THE SAME NUMBER OF CARBON ATOMS





n	$\Delta I^{OV\text{-}1-OV\text{-}25}$	R	$\Delta I^{OV\text{-}1-OV\text{-}25}$	$d\Delta I$
0	670	Propyl	565	105
1	658	Butyl	554	104
2	638	Pentyl	554	84
3	629	Hexyl	544	85

For example, we obtained curves with a similar course to the retention index values for the alkyl homologues of benzoic acid published by Pias and Gasco [9] or those of the N-alkylaniline derivatives investigated by Váradi and Tóth [10].

Subsequently, the data on the aliphatic and cycloaliphatic 2,3-substituted compounds (I, ΔI, dI/dz) were compared in a search for a relationship between the retention properties and the polarity of aliphatic and cyclic compounds with the same number of carbon atoms (Table II).

For the same number of carbon atoms, it can be assumed that the extents of the inductive effect towards the quinazolone ring are nearly the same, and any difference is an expression of the difference in the steric effects of the freely rotating aliphatic methylene groups relative to the rigid or flexible ring. From a comparison of the tricyclic and the corresponding disubstituted aliphatic quinazolones, this "ring effect" cause a difference of *ca* 100–150 i.u., *i.e.*, for the same number of carbon atoms the ring closure causes a polarity change equivalent to that of about one methylene group. The correlations found are well supported by the previously published pK_s and log P values for the compounds [5,6]. The pK_s values, which change in parallel with the electronic changes, agree well, whereas the partition coefficient values, which express the steric and polarity changes, exhibit a difference corresponding to one methylene group, as expressed numerically by the gas chromatographic method.

REFERENCES

1 S. Johne, *Prog. Drug Res.*, 26 (1982) 259.
2 A. H. Amin, D. R. Mehta and S. S. Samarth, *Prog. Drug Res.*, 14 (1970) 218.
3 I. Hermecz, L. Vasvári-Debreczy, Á. Horváth, S. Virágh, T. Breining and J. Kökösi, *Ger. Pat.*, 3 339 635; *C.A.*, 101 (1984) 130 705.
4 I. Hermecz, L. Vasvári-Debreczy, Á. Horváth, M. Balogh, J. Kökösi, C. De Vos and L. Rodrigez, *J. Med. Chem.*, 30 (1987) 1543.

5 K. Hankó-Novák, M. Józan, Gy. Szász, J. Kökösi and I. Hermecz, *Acta Pharm. Hung.*, 54 (1984) 280.
6 K. Hankó-Novák, Gy. Szász, O. Papp, J. Vámos and I. Hermecz, *Acta Pharm. Hung.*, 53 (1983) 208.
7 O. Papp, G. Szász, J. Kökösi and I. Hermecz, *J. Chromatogr.*, 537 (1991) 365.
8 W. L. F. Armarego, *Adv. Heterocycl. Chem.*, 1 (1963) 93.
9 B. Pias and L. Gasco, *J. Chromatogr.*, 104 (1975) D14.
10 A. Váradi and T. Tóth, *Magy. Kém. Foly.*, 80 (1974) 41.