Hindered Internal Rotation About Aryl C—N Bonds in Aryl Substituted Heterocyclic Compounds: 3-Aryl-2-benzyl-4(3*H*)-quinazolinones

LAWRENCE D. COLEBROOK AND H. GWYNNE GILES
Department of Chemistry, Sir George Williams Campus, Concordia University, Montreal, Quebec H3G 1M8
Received November 13, 1974[1]

LAWRENCE D. COLEBROOK and H. GWYNNE GILES. Can. J. Chem. **53**, 3431 (1975).

The proton magnetic resonance spectra of a number of 3-aryl substituted 2-benzyl-4(3*H*)-quinazolinones indicate that internal rotation about the aryl C—N bond is highly hindered. Substantial free energy barriers (18.9–19.8 kcal/mol) have been measured even when the aryl groups lack bulky *ortho* substituents.

LAWRENCE D. COLEBROOK et H. GWYNNE GILES. Can. J. Chem. **53**, 3431 (1975).

Les spectres r.m.n. d'un certain nombre d'aryl (substitués)-3 benzyl-2 (3*H*)-quinazolinones-4 indiquent que la rotation interne autour du lien C(aryl)—N est très empêchée. On a mesuré des barrières importantes (18.9–19.8 kcal/mol) d'énergie libre même lorsque les groupes aryles ne portent pas de substituants *ortho* volumineux.

[Traduit par le journal]

As part of a study of restricted internal rotation about aryl C—N bonds in aryl substituted heterocyclic compounds (1–5)[2], we have prepared a series of 3-aryl substituted 2-benzyl-4(3*H*)-quinazolinones and have investigated their proton magnetic resonance spectra. Of particular interest are the barriers to internal rotation of the 3-aryl groups and their dependence on the nature of the 3-aryl group substituents. The steric barriers to aryl group rotation in these compounds are expected to be high, since, in the transition states for rotation there should be severe crowding between the *ortho* substituents on the 3-aryl group and the heterocyclic ring substituents adjacent to the 3-position, *i.e.* the benzyl group in the 2-position, and the oxygen atom of the carbonyl group. Large dihedral angles between the 3-aryl and the heterocyclic moieties are expected in the conformational ground states (4), which are enantiomeric in the compounds studied.

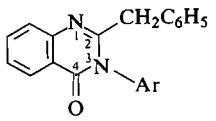
The 3-aryl-2-benzyl-4(3*H*)-quinazolinones are stereochemically analogous to biphenyls, and undergo similar interconversion processes between enantiomeric rotational isomers. Other examples of compounds in which the biphenyl-like restriction to rotation about C—N bonds linking two cyclic moieties is predominantly steric in origin have been reported: 2-aryl-1,4-dihydro-3(2*H*)-isoquinolinones (6), 3-aryl-3,4-dihydro-2*H*-1,3-benzoxazines (7), 2-methyl- and 2,2-dimethyl-1-aryl-1,2-dihydro-4,6-diamino-*s*-triazines (1, 2), 3-arylhydantoins and 3-aryl-2-thiohydantoins (1–5), and 1-arylhydantoins (3, 5). The stereochemistry, based on the biphenyl model, of the process of torsion about the C—N pivot bonds of such compounds has been discussed in detail by Shvo *et al.* (6).

In addition to acting as a steric blocking group to rotation of the 3-aryl group, the 2-benzyl substituent functions as a 'probe' to enable the restricted rotational process to be detected in the proton magnetic resonance spectrum. Provided that the substitution pattern on the 3-aryl group is unsymmetric, the benzylic methylene protons in these compounds are diastereotopic, and may be expected to give rise to an AB quartet if rotation of the 3-aryl group is slow on the n.m.r. time scale. If aryl group rotation is fast on the n.m.r. time scale, the AB quartet should collapse to a singlet. Rate constants should be obtainable by complete line shape analysis of the partially collapsed methylene group signals at intermediate rates of rotation (8), providing that the chemical shift difference is sufficiently large. Rotation of the 3-aryl group is the only conformational exchange process in these compounds which can result in exchange of the environments of the benzylic methylene protons, causing collapse of the AB quartets.

[1]Revision received August 1, 1975.
[2]Reference 2 contains a preliminary report of some of the material in this paper.

Results and Discussion

With a suitable choice of solvent, all eight compounds prepared for this investigation exhibited AB quartets, arising from the benzylic methylene protons, in their 100 MHz n.m.r. spectra at normal probe temperatures (about 26 °C), indicating that rotation of the 3-aryl group about the aryl C—N bond was slow on the n.m.r. time scale. The chemical shifts between the benzylic methylene protons showed a strong solvent dependence, which is not easily predictable. Thus, the 3-(2-tolyl), **4**, and the 3-(2-fluorophenyl), **5**, compounds exhibited



1 Ar = 2-chloro-6-methylphenyl
2 Ar = 2-bromophenyl
3 Ar = 2-chlorophenyl
4 Ar = 2-tolyl
5 Ar = 2-fluorophenyl
6 Ar = β-naphthyl
7 Ar = 3-bromophenyl
8 Ar = 3-acetylphenyl

no chemical shift difference between the benzylic methylene protons in nitrobenzene solution. The chemical shift differences for the remaining six compounds ranged from 0.088–0.295 p.p.m. These two compounds showed chemical shift differences of 0.057 and 0.143 p.p.m., respectively, in bromoform solution. In view of the high rotational barriers exhibited in nitrobenzene solution by all the other compounds (**1–3**) with *ortho*-substituted 3-aryl groups, and the behavior of these two compounds in bromoform solution, the observation of a singlet for the benzylic methylene protons cannot be attributed to the effects of fast rotation of the 3-aryl group.

Compounds with ortho-Substituted 3-Aryl Groups

Attempts to measure the rate of rotation of the 3-aryl groups by line shape analysis of the AB quartets at elevated temperatures failed for all those compounds (**1–5**) with *ortho*-substituted 3-aryl groups. No indications of collapse of the AB quartets through time averaging were detectable at the highest temperatures employed (150–187 °C), even for compounds with small blocking substituents, such as fluoro, in an *ortho* position.

Minimal possible values for the free energies of activation (Table 1) were estimated from rate constants (9) calculated from the chemical shifts and coupling constants (10) on the assumption that the spectra had collapsed to the coalescence points at the highest temperatures employed. Since no signs of incipient temperature dependence were observed at these sample temperatures, it may safely be assumed that the true free energies of activation for 3-aryl group rotation in these compounds are considerably higher than those shown in Table 1. These figures suggest that compounds of this type should be resolvable and have substantial optical stability at normal temperatures.

Compounds with meta-Substituted 3-Aryl Groups

In view of the high barriers to internal rotation in those compounds with blocking substituents in the ortho positions of the 3-aryl groups, three compounds (**6–8**) were prepared in which the only blocking substituents present in the *ortho*-positions are hydrogen atoms (2). Barriers to internal rotation in these compounds would be expected to be much lower than in the other series. The steric requirements of one of the *ortho* hydrogen atoms may be increased by buttressing with the adjacent substituent. This situation is unavoidable since an unsymmetrical substitution pattern on the 3-aryl group is necessary to render the benzylic methylene protons diastereotopic.

These compounds showed well resolved AB quartets arising from the benzylic methylene protons, with chemical shift differences of 0.088–0.132 p.p.m. (nitrobenzene solutions). When the samples were warmed the AB quartets collapsed to singlets, with coalescence temperatures in the range 94–116 °C (Table 1), indicating fast internal rotation about the aryl C—N bonds on the n.m.r. time scale. The original spectra reappeared when the samples were cooled.

Although, in principle, a complete set of activation parameters should be obtainable by complete line shape analysis of the partially collapsed AB quartets over a range of temperatures, this was not considered practicable in the present case. The chemical shifts between the diastereotopic methylene protons are small, and the nuclei tightly coupled (Table 1), limiting the temperature range over which the spectra show sufficient temperature dependence for accurate line shape analysis. In such cases only

TABLE 1. Proton magnetic resonance[a] and activation parameters for 2-benzyl-3-aryl-4(3*H*)-quinazolinones

Compound	Solvent	Benzylic protons δ_B[d]	Benzylic protons δ_A[d]	Benzylic protons $\lvert J_{AB}\rvert$(Hz)	Coalescence temperature (°C)	$\Delta G^{\ddagger}$ (kcal/mol)
1	Nitrobenzene	3.916	3.621	14.7	187[b]	23.7[c]
2	Nitrobenzene	3.919	3.709	14.8	177[b]	23.3[c]
3	Nitrobenzene	3.923	3.754	15.0	177[b]	23.3[c]
4	Bromoform[e]	3.833	3.776	14.5		[f]
5	Bromoform[e]	3.966	3.823	15.1	150[b]	21.9[c]
6	Nitrobenzene	3.958	3.826	15.1	116	19.8±0.3
7	Nitrobenzene	3.854	3.766	15.1	94	18.9±0.3
8	Nitrobenzene	3.966	3.861	15.0	102	19.2±0.3

[a]100 MHz.
[b]Highest temperature employed. No collapse observed.
[c]Minimum value of $\Delta G^{\ddagger}$ at the specified temperature.
[d]Chemical shifts in p.p.m. from TMS.
[e]The benzylic protons give rise to singlets in nitrobenzene solution.
[f]Not calculated because of the small chemical shift difference.

TABLE 2. Melting points, yields, elemental analyses, and carbonyl stretching frequencies of 3-aryl-2-benzyl-4(3*H*)-quinazolinones

Compound	Melting point (°C)	Yield (%)	Formula	Calculated (%) C	Calculated (%) H	Calculated (%) N	Found (%) C	Found (%) H	Found (%) N	C=O stretch (cm^{-1})[a]
1	152	6	$C_{22}H_{17}ClN_2O$	73.23	4.75	7.76	72.97	4.15	7.69	1670
2	130	50	$C_{21}H_{15}BrN_2O$	64.46	3.86	7.16	64.77	3.73	6.93	1685
3	111	12	$C_{21}H_{15}ClN_2O$	72.73	4.36	8.08	72.45	4.42	7.97	1690
4	113	30	$C_{22}H_{18}N_2O$	80.96	5.56	8.58	81.05	5.37	8.58	1665
5	133	15	$C_{21}H_{15}FN_2O$	76.35	4.58	8.48	76.46	4.73	8.60	1675
6	136	20	$C_{25}H_{18}N_2O$	82.85	5.01	7.73	83.11	4.81	7.69	1675
7	110	8	$C_{21}H_{15}BrN_2O$	64.46	3.86	7.16	64.28	3.66	7.15	1675
8	129	6	$C_{23}H_{18}N_2O_2$	77.95	5.12	7.90	78.10	5.17	7.80	[b]

[a]KBr discs.
[b]Overlapped by acetyl carbonyl band.

free energies of activation are likely to be accurate. Values of $\Delta G^{\ddagger}$ at the coalescence temperatures, calculated from rate constants (9) obtained by computer simulation of the line shapes (11) in the coalescence region, are reported in Table 1.

Compensation for the poor blocking ability of the *ortho* hydrogen atoms in these compounds is provided by the high steric requirements of the 2-benzyl group and the oxygen atom of the carbonyl group in the 4-position, resulting in severe steric interaction between the two moieties in the transition states for aryl group rotation. A large contribution to the steric barrier to rotation appears to result from the geometry at the 2-position of the hetero ring. Coplanarity between the bond joining the benzylic carbon and C-2 with the hetero ring maximizes steric interaction between the benzyl group and the ortho substituents on the 3-aryl group in the transition states for rotation (assumed to be approximately planar). In closely related compounds with the N-1—C-2 bond reduced, so that the hydridization at C-2 is formally sp^3, the barriers to rotation are considerably lower (12).

Experimental

Preparation of Materials

The 2-benzyl-3-aryl-4(3*H*)-quinazolinones were prepared by an adaptation of the method of Klosa (13). *N*-(Phenylacetyl)anthranilic acid (prepared by the method of de Diesbach *et al.* (14)) was employed as the precursor in all cases. Reaction of this compound with the appropriate aryl amine was carried out in the presence of polyphosphoric acid. Normally, two recrystallizations from methanol yielded analytically pure products. However, **8** required chromatography before the pure material was obtained.

Experimental details of two representative syntheses are given. No attempts were made to maximize yields. Analytical data are shown in Table 2. The structures were confirmed by n.m.r. and i.r. spectra. Elemental analyses were performed either by Galbraith Laboratories, Knoxville, Tennessee, U.S.A., or by Alfred Bernhardt, Mikroanalytisches Laboratorium, West Ger-

many. Infrared spectra were taken (KBr discs) on a Perkin-Elmer 457 spectrophotometer, and melting points on a Mettler FP1 apparatus.

2-Benzyl-3-(2-naphthyl)-4-(3H)-quinazolinone, **6**

N-(Phenylacetyl)anthranilic acid (10.0 g, 0.0392 mol), 2-naphthylamine (Eastman) (3.26 g, 0.0228 mol) and polyphosphoric acid (40 g) were heated to 180 °C with stirring, and kept at that temperature for 30 min. After cooling, the solution was poured into a concentrated sodium carbonate solution. When neutralization was complete, the product was extracted with chloroform (100 ml). When the resulting solution was washed with hydrochloric acid (6 *N*, 50 ml) a white precipitate (probably the amine salt) formed in the organic layer. This precipitate was removed by filtration. The process of washing with hydrochloric acid was repeated until no more precipitate formed. The chloroform layer was then neutralized with sodium carbonate solution, washed, and dried over molecular sieves (British Drug Houses, type 4A). The chloroform was removed under vacuum to yield an oil that solidified after standing for 30 min. The crude product was recrystallized three times from methanol to give pale needles that were then dried under vacuum.

2-Benzyl-3-(3-acetylphenyl)-4(3H)-quinazolinone, **8**

N-(Phenylacetyl)anthranilic acid (10.0 g, 0.0392 mol), *m*-aminoacetophenone (K and K) (5.29 g, 0.0392 mol), and polyphosphoric acid (44 g) were heated to 180 °C with stirring and kept at that temperature for 25 min. After cooling, the solution was poured into a concentrated sodium carbonate solution. When neutralization was complete the product was extracted with chloroform (100 ml) and the resulting solution was washed with hydrochloric acid (6 *N*, 50 ml) to remove any unreacted amine, and was then washed with sodium bicarbonate solution. The organic layer was separated and the chloroform solvent was removed under vacuum, yielding a brown oil. The oil was dissolved in an ether–ethanol (50:50) mixture and was chromatographed on silica gel (100 g, 60–120 mesh, British Drug Houses). The column was first eluted with ether (fraction 1, 120 ml, orange; fraction 2, 80 ml, black; fraction 3, 130 ml, orange), then ethanol (fraction 4, 60 ml, yellow; fraction 5, 120 ml, orange), and finally chloroform (fraction 6, 500 ml, yellow). The solvent was evaporated from fraction 2 to yield a red oil. The oil was dissolved in acetone and the solution was poured into water, yielding a yellow suspension. After 2 days a yellow solid which had formed was filtered off and dried under vacuum, then recrystallized from methanol.

Magnetic Resonance Measurements

Proton magnetic resonance spectra were taken using a Varian HA-100 spectrometer operating in the field sweep mode and employing the standard variable temperature equipment. The AB quartets arising from the benzylic methylene protons of the substituent in the 2-position were recorded at maximum convenient scale expansion. Temperatures, believed to be accurate to ± 2°C, were determined immediately after each spectrum was taken by measuring the peak separation of a standard Varian ethylene glycol sample.

Because of the high barriers to internal rotation in this series of compounds and the consequent high temperatures at which spectral measurements must be made, it is necessary to use high boiling solvents. The choice of solvent is important, since the chemical shift differences resulting from anisotropic shielding by the aryl groups may be small and solvent dependent. For example, the room temperature spectrum of the 3-(3-bromophenyl) compound, **7**, in bromoform solution shows a singlet rather than an AB quartet in the methylene region at $\delta 3.85$, although quartets appear when nitrobenzene or deuterochloroform solutions are used. In the case of the 3-(2-fluorophenyl) compound, **5**, AB quartets were exhibited by deuterochloroform and bromoform solutions, and singlets by nitrobenzene, DMSO-d_6, and 2-chloropyridine solutions. Nitrobenzene was found to be a useful high boiling solvent for this series, but, as noted, it could not be used in all cases.

This work was supported by grants from the National Research Council of Canada.

1. W. E. Bentz, L. D. Colebrook, J. R. Fehlner, and A. Rosowsky. Chem. Commun. 974 (1970).
2. L. D. Colebrook, H. G. Giles, and A. Rosowsky. Tetrahedron Lett. 5239 (1972).
3. L. D. Colebrook, H. G. Giles, A. Granata, S. Icli, and J. R. Fehlner. Can. J. Chem. **51**, 3635 (1973).
4. P. H. Bird, L. D. Colebrook, A. R. Fraser, and H. G. Giles. Chem. Commun. 225 (1974).
5. L. D. Colebrook, S. Icli, and F. H. Hund. Can. J. Chem. **53**, 1556 (1975).
6. Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban. J. Am. Chem. Soc. **89**, 4910 (1967).
7. S. Brownstein, E. C. Horswill, and K. U. Ingold. Can. J. Chem. **47**, 3243 (1969).
8. G. Binsch. *In* Topics in stereochemistry. Vol. III. *Edited by* E. R. Eliel and N. L. Allinger. Interscience Publishers, New York. 1968. p. 97.
9. W. J. Moore. Physical chemistry. 3rd ed. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. 1964. Chapt. 8.
10. R. J. Kurland, M. B. Rubin, and W. B. Wise. J. Chem. Phys. **40**, 2426 (1964).
11. S. Alexander. J. Chem. Phys. **37**, 967 (1962).
12. J. R. Fehlner. Ph.D. Thesis, University of Rochester, Rochester, New York. 1970.
13. J. Klosa. J. Prakt. Chem. **20**, 283 (1963).
14. H. de Diesbach, J. Gross, and W. Tschannen. Helv. Chim. Acta, **34**, 1050 (1951).