Some Benzazocinecarboxylic Acids as Potential Anti-inflammatory Agents

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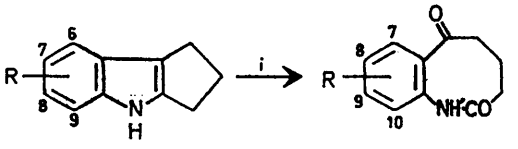
A series of substituted benzazocine acids (VIa—h) have been prepared by a one-carbon homologation procedure from the benzazocine-2,6-diones (IIa—f). A novel rearrangement of the intermediate aldehyde (Va) to 3,4-dihydrocarbazol-1(2*H*)-one was discovered. The anti-inflammatory activity of the acids (VIa—h) was investigated.

THE need for better, more specific, anti-rheumatic drugs has led to the synthesis of a series of acid derivatives of benzazocine. This programme was based on the supposition that some of the side effects inherent in certain clinically important agents could be ascribed to their heteroaryl skeletons or metabolites retaining these skeletons. Some derivatives of phenylacetic acid are exceptionally active anti-inflammatory agents; these include (+)-*S*-2-[3-chloro-4-cyclohexylphenyl]propionic acid [1] and (+)-(*S*)-6-chloro-5-cyclohexylindane-1-carboxylic acid.[2] It was thought that structural modification of such compounds could produce interesting and useful new anti-inflammatory agents. Thus initially the effect on the biological activity of altering the nature of the cycloalkyl ring in the indane derivative was investigated. The introduction of an amidic nitrogen atom γ to the acid function was of particular interest in that a formal resemblance to the fenamic acid series [3] of anti-inflammatory compounds was established. The lipophilic character of the acids was systematically modified by appropriately substituting the amidic nitrogen atom with alkyl and aralkyl radicals. The amide group was also alkylated with a 2,6-dichlorobenzyl group, such that the newly introduced aromatic ring would assume an antiplanar conformation relative to the original aromatic ring, thus realising the optimal configuration for fitting the hypothetical anti-inflammatory receptor proposed by Scherrer, Winder, and Short.[4]

Diazotisation of a series of substituted anilines followed by reduction of the diazonium species gave a corresponding series of hydrazines. These were condensed with cyclopentanone and the intermediate hydrazones were cyclised under acidic conditions to yield the substituted cyclopent[*b*]indoles (Ia—f). In the case of biphenyl-3-ylhydrazine a mixture containing approximately equal amounts of the two possible cyclopent[*b*]indoles (Ie and f) was formed; the 6-phenyl isomer (If) was isolated in pure form. Immediate oxidative cleavage, by sodium periodate, of the frequently unstable cyclopent[*b*]indoles (Ia—f) gave the benzazocine-2,6-diones (IIa—f). The 6- and 8-phenylcyclopent[*b*]indole mixture gave a mixture of benzazocine-2,6-diones (IIf and e), which was separated by fractional crystallisation. The lower melting 9-phenyl isomer (IIe) exhibited a low-field aromatic doublet (τ 1.85, J 8 Hz) characteristic of H-7 adjacent to the ketonic carbonyl group.

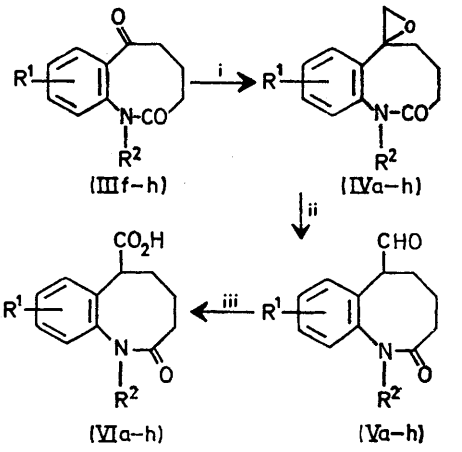


(Ia—f) (IIa—f)

a; R = H
b; R = 7-Pr^i
c; R = 7-PhCH$_2$·O
d; R = 7-Ph
e; R = 8-Ph
f; R = 6-Ph

} Numbering as in (I) transformation required for (II)

Reagents: i, $NaIO_4$, MeOH–H_2O–THF



(IIIf-h) (IVa-h) (VIa-h) (Va-h)

a; $R^1 = R^2 = H$
b; R^1 = 8-Pr^i, $R^2 = H$
c; R^1 = 8-PhCH$_2$·O, $R^2 = H$
d; R^1 = 8-Ph, $R^2 = H$
e; R^1 = 9-Ph, $R^2 = H$
f; $R^1 = H$, R^2 = Me
g; $R^1 = H$, R^2 = PhCH$_2$
h; $R^1 = H$, R^2 = 2,6-$Cl_2C_6H_3$·CH_2

Reagents: i, $Me_3S^+I^-$–NaH; ii, BF_3,Et_2O–THF; iii, CrO_3–Me_2CO

The carboxy-group was introduced into the benzazocine-2,6-dione system by reaction of the oxo-amides (IIa—e) with the ylide derived from trimethylsulphonium iodide.[5] The ylide was generated in dimethyl sulphoxide solution in the presence of the oxo-amide by using 2 mol of sodium hydride for each mol of the oxo-amide, the remaining mol of base being consumed in displacing the amidic proton. Rearrangement of the oxirans (IVa—e) with boron trifluoride–ether complex in tetrahydrofuran gave the corresponding aldehydes (Va—e), which in view of their observed lability were directly oxidised with

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[3] P. F. Juby and T. H. Hudyma, *Ann. Reports Medicin. Chem.*, 1972, **7**, 211.
[4] R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, 9th National Medicinal Chemistry Symposium of the American Chemical Society, June 1964, p. 11a.
[5] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.* 1962, **84**, 3782.

Jones' reagent [6] at 0 °C to the arylacetic acids (VIa—e) in moderate yields.

When the unsubstituted oxo-amide (IIa) was treated with an excess of ylide the major product was the *N*-methyl oxiran (IVf). Rearrangement of the oxiran (IVf) gave the intermediate aldehyde which was immediately oxidised to the *N*-methyl acid (VIf). Similarly, but by insertion of a separate benzylation step, the *N*-benzyl acids (VIg and h) were prepared.

Rearrangement of the oxiran (IVa) with boron trifluoride–ether complex in methylene chloride gave very little isolable aldehyde (Va); 3,4-dihydrocarbazol-1(2*H*)-one was obtained instead. The product was identified by spectroscopic methods and confirmed by comparison with a sample prepared by Fischer cyclisation of the monophenylhydrazone of cyclohexane-1,2-dione.[7] The rearrangement may be rationalised by invoking a transannular cyclisation of the aldehyde, transiently observed by t.l.c., involving its aldehydic carbon atom and the amidic nitrogen atom, followed by a dehydration and bond migration.

The n.m.r. spectra of the benzazocine derivatives (Table) confirmed the assigned structures. The spectrum of the *N*-substituted benzazocine derivative (IVf) showed two readily distinguishable AB patterns for the protons attached to the oxiran ring, and also two closely spaced *N*-methyl absorptions in [$^2H_6$]dimethyl sulphoxide solution at room temperature. This pattern, while discernible in deuteriochloroform solution, was not clearly resolved. The relative intensities of these duplicate absorptions were temperature-dependent, the *N*-methyl absorptions having completely coalesced at 100 °C. This can be interpreted as being due to slow (on the n.m.r. time scale) interconversion of two distinct conformers of the eight-membered ring. The nature of these species is further defined by the observation of a small coupling (J 1 Hz) on the high-field portion of the AB pattern of the major conformer; furthermore the *N*-methyl absorption of this conformer was at lower field, consistent with the presence of the methyl group in the deshielded area adjacent to the benzenoid ring.

The benzazocine acids (VIa—h) were evaluated as potential anti-inflammatory agents on the rat adjuvant arthritis [8] and carrageenin oedema [9] screens at 50 and 100 mg kg^{-1}, respectively. No significant activity was detected.

EXPERIMENTAL

M.p.s were determined with a Buchi oil-bath apparatus. I.r. spectra (Nujol mulls) were recorded on a Perkin-Elmer 157 spectrophotometer. N.m.r. spectra were determined with a Varian A-60 or HA-100 spectrometer for solutions in deuteriochloroform unless otherwise stated. Mass spectra were measured with a Hitachi RMU-6E or an A.E.I. MS-9 double-focusing spectrometer operating at 70 eV.

Substituted Phenylhydrazines.—These were prepared by reduction with sodium dithionite of the aniline-derived diazonium salts and were isolated as their hydrochloride salts. The phenylhydrazine hydrochlorides were characterised by m.p.s: p-*isopropyl*-, m.p. 218—220°; p-*benzyloxy*-, m.p. 217—218° (lit.,[10] 219°); p-*phenyl*-, m.p. 212—214° (lit.,[11] 213—214°); m-*phenyl*-, m.p. 176—178° (lit.,[11] 175—176°).

The Cyclopent[b]*indoles* (Ia *and* b).—These were prepared by the method of ref. 12. The 7-isopropyl derivative (Ib) (71% yield) had m.p. 85—90° (from aqueous methanol).

7-*Benzyloxy*-1,2,3,4-*tetrahydrocyclopent*[b]*indole* (Ic).—A solution of *p*-benzyloxyphenylhydrazine hydrochloride (50.2 g, 0.2 mol) and cyclopentanone (33.6 g, 0.4 mol) in ethanol (1 500 ml) was heated on a steam-bath for 5 h. The hot mixture was filtered and the filtrate evaporated to *ca.* 750 ml whereupon the *indole* (Ic), m.p. 110—112° (Found: N, 5.2. $C_{18}H_{17}NO$ requires N, 5.3%), crystallised (23.2 g). Evaporation of the mother liquor to dryness, chromatography of the residue on silica gel (600 g), and elution with toluene, gave more product (12.1 g), m.p. 114—115° (total yield 67%).

1,2,3,4-*Tetrahydro*-7-*phenylcyclopent*[b]*indole* (Id).—Biphenyl-4-ylhydrazine (4.8 g) and cyclopentanone (2.19 g) were mixed and heated on a steam-bath for 15 min. Concentrated sulphuric acid (7 ml) in water (120 ml) was added and the mixture heated for a further 25 min. After cooling in an ice-bath, the oily solid which separated was filtered off. Chromatography on silica gel (70 g) and elution with toluene gave the indole (Id) (1.5 g).

1,2,3,4-*Tetrahydro*-6-*and*-8-*phenylcyclopent*[b]*indole* (If *and* e).—A solution of biphenyl-3-ylhydrazine (39.3 g) and cyclopentanone (36.9 g) in ethanol (700 ml) was heated on a steam-bath for 3 h. The hot mixture was filtered and the filtrate evaporated to *ca.* 150 ml whereupon the 6-phenyl isomer, m.p. 210—212° (13.3 g), crystallised. Evaporation of the mother liquor to dryness, chromatography of the residue on silica gel (1 kg), and elution with toluene, gave a crystalline mixture of 6- and 8-phenyl isomers (29.9 g).

Substituted Benzazocine-2,6-*diones* (IIa—f). A solution of the indole (0.066 mol) in methanol (250 ml) and tetrahydrofuran (100 ml) was added to sodium periodate (0.132 mol) in water (130 ml) at room temperature. The solution became warm and sodium iodate was deposited. After 2 h the solution was diluted with water (500 ml) and extracted with methylene chloride (4 × 150 ml). The combined extracts were washed with water (2 × 100 ml), dried ($MgSO_4$), filtered, and evaporated. Crystallisation of the residue gave the following [1]benzazocine-2,6(1*H*,3*H*)-diones: 4,5-dihydro-, m.p. 171—171.5° (from carbon tetrachloride) (lit.,[13] m.p. 170—170.5°); 4,5-*dihydro*-8-*isopropyl*-, m.p. 181—183° (from ethyl acetate) (Found: C, 72.7; H, 7.5; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); 8-*benzyloxy*-4,5-*dihydro*-, m.p. 170—171° (from toluene) (Found: C, 73.3; H, 5.7; N, 5.0. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); 4,5-*dihydro*-8-*phenyl*-, m.p. 214—216° (from toluene) (Found: C, 76.7; H, 5.7; N, 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%); 4,5-*dihydro*-9-*phenyl*-, m.p. 198—199° (from toluene)

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(Found: C, 76.9; H, 5.6; N, 5.3. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%); and 4,5-*dihydro*-7-*phenyl*-, m.p. 216—217° (from toluene) (Found: C, 77.2; H, 5.9; N, 5.0. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%).

Alkylation of the Benzazocine-2,6-*dione* (IIa).—Sodium hydride (60%; 10 mmol) was washed free of mineral oil with petroleum (b.p. 40—60°; 3 × 10 ml) and suspended in dimethylformamide (30 ml), and the amide (IIa) (5 mmol) was added in portions with stirring under nitrogen. After 10 min the benzyl bromide (5 mmol) was added and an exothermic reaction was observed. After 3 h the mixture was diluted with water and extracted with ether (3 × 80 ml). The extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. Crystallisation of the residue gave the following 4,5-dihydro[1]benzazocine-2,6(1*H*,3*H*)-diones: 1-benzyl-, isolated as an oil which partially crystallised; 1-(2,6-*dichlorobenzyl*)-, m.p. 137—138° (from cyclohexane) (Found: C, 62.0; H, 4.3; N, 3.9. $C_{18}H_{15}Cl_2NO_2$ requires C, 62.1; H, 4.3; N, 3.9%).

Substituted Spiro[*benzazocin*-6(3H),2′-*oxiran*]-2(1H)-*ones* (IVa—h).—Sodium hydride (50 mmol) was washed free of mineral oil with petroleum (b.p. 40—60°; 3 × 7 ml), and dimethyl sulphoxide (75 ml) and the ketone (20 mmol) were added under nitrogen. The mixture was stirred to dissolve the ketone. Trimethylsulphonium iodide [5] (30 mmol) was added rapidly and the mixture was stirred for 4 h, then poured into a large excess of brine and extracted with toluene (3 × 200 ml). The extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. Crystallisation of the residue gave the following spiro[benzazocin-6(3*H*),2′-oxiran]-2(1*H*)-ones: 4,5-*dihydro*-, m.p. 174—176° (from cyclohexane–toluene) (Found: C, 71.0; H, 6.4; N, 6.7. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45, N, 6.9%); 4,5-*dihydro*-8-*isopropyl*-, m.p. 150—160° (from cyclohexane) (Found: C, 73.5; H, 8.0; N, 5.4. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); 8-*benzyloxy*-4,5-*dihydro*-, m.p. 168—169° (from toluene) (Found: C, 73.6; H, 6.2; N, 4.3. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%); 4,5-*dihydro*-8-*phenyl*-, m.p. 200—202° (from toluene) (Found: C, 77.4; H 6.2; N, 4.8. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.2; N, 5.0%); 4,5-*dihydro*-9-*phenyl*-, m.p. 191—193° [from toluene–petroleum (b.p. 60—80°)] (Found: C, 77.1; H, 6.1; N, 4.9. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); 4,5-*dihydro*-1-*methyl*-, m.p. 108—110° (from cyclohexane) (Found: C, 71.9; H, 7.0; N, 6.4. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%); 1-*benzyl*-4,5-*dihydro*-, m.p. 159—160° (from cyclohexane) (Found: C, 78.1; H, 6.7; N, 4.6. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8%); 1-(2,6-*dichlorobenzyl*)-4,5-*dihydro*-, m.p. 144—146° (from cyclohexane) (Found: C, 62.8; H, 4.9; N, 3.7. $C_{19}H_{17}Cl_2NO_2$ requires C, 63.0; H, 4.7; N, 3.9%).

Substituted Benzazocine-6-*carbaldehydes* (Va—h). To a solution of the oxiran (10 mmol) in tetrahydrofuran (125 ml) cooled to 0 °C was added boron trifluoride–ether complex (0.55 ml). After 1 h the solution was diluted with aqueous 10% sodium carbonate (*ca.* 100 ml) and extracted with ethyl acetate (3 × 150 ml). The extracts were washed with brine (2 × 50 ml), dried ($MgSO_4$), and evaporated [$\nu_{max.}$ 2 720 (CH) and 1 720 cm^{-1} (C=O)]. On account of the instability of these aldehydes, they were oxidised immediately.

Substituted Benzazocine-6-*carboxylic Acids* (VIa—h).—A solution of the aldehyde (10 mmol) in acetone (110 ml) was cooled to −5 °C and treated dropwise during 10 min with Jones' reagent [6] (*ca.* 4 ml). After stirring for a further 25 min at 0 °C the excess of oxidant was destroyed with propan-2-ol, and the solution was diluted with water and extracted with ethyl acetate (3 × 150 ml). The extracts were washed with brine (2 × 25 ml), dried ($MgSO_4$), and evaporated. Crystallisation of the residue gave the following 1,2,3,4,5,6-hexahydro[1]benzazocine-6-carboxylic acids: 2-*oxo*-, m.p. 236—237° (from acetonitrile) (Found: C, 65.5; H, 5.9; N, 6.2. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%); 8-*isopropyl*-2-*oxo*-, m.p. 217—219° (from ethyl acetate) (Found: C, 68.6; H, 7.3; N, 5.1. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.4%); 8-*benzyloxy*-2-*oxo*-, m.p. 217—218° (from acetonitrile) (Found: C, 69.9; H, 5.8; N, 4.6. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 6.0; N, 4.3%);

Chemical shifts (τ values; solvent $CDCl_3$; *J* in Hz)

	NH and NMe	H-7	Aromatic	CH_2	Oxiran O·CH_2 [a]		H-6	Other
(II) a	0.28	1.82 (*J* 8)	2.2—2.9	6.9—8.2				
b	0.40	1.98 (*J* 2)	2.4—2.9	7.0—8.0				8.75 [b]
c	0.62	2.28 (*J* 2)	2.5—2.9	7.0—7.9				4.92 [c]
d	0.30	1.60 (*J* 2)	2.1—2.9	6.9—7.9				
e [d]		1.85 (*J* 8)	2.1—2.6	7.0—8.0				
f	1.1	1.85 (*J* 8)	2.5—2.9	7.5—8.2				
(III) g		2.1 (*J* 8)	2.3—2.9	7.0—8.3				4.68, 5.38 [e]
h		2.1 (*J* 7)	2.4—2.9	6.8—8.4				4.38, 4.80 [e]
(IV) a	0.7	2.45 (complex)	2.6—3.0	7.6—8.4	7.10	7.4		
b	1.5	2.6 (*J* 2)	2.8—3.0	7.7—8.5	7.13	7.35		8.76 [b]
c	1.42		2.5—3.2	7.6—8.4	7.12	7.28		4.95 [c]
d	1.1	2.17 (*J* 1.6)	2.2—2.9	7.5—8.3	7.0	7.24		
e	1.45		2.2—2.8	7.3—8.2	6.94	7.16		
f	6.70		2.3—2.8		7.08	7.35		
g			2.4—2.9	7.5—8.5	7.14	7.46		5.05(s) [e]
h			2.3—3.0	7.5—8.3	7.05	7.35		4.21, 5.1 [e]
(VI) a	0.83		2.5—3.0	7.4—8.5			6.35	
b [d]	0.52 [f]		2.7—3.1	7.8—8.7			6.4—6.8br	8.82 [b]
c [d]	0.55		2.3—3.2	7.4—8.8			6.60	4.94 [c]
f	6.78		2.5—2.8	7.5—8.7			5.95	
g			2.5—2.9	7.4—8.4			6.75	4.8, 5.22 [e]
h [d]			2.5—3.0	7.3—8.5			6.55	4.75(s) [e]

[a] AB pattern, J_{AB} 5 Hz. [b] d, *J* 8 Hz, CMe_2. [c] s, ArCH_2·O. [d] Solvent $(CD_3)_2SO$. [e] Benzylic CH_2 as an AB pattern unless otherwise specified, J_{AB} 13—14 Hz. [f] Exchangeable with D_2O.

2-*oxo*-8-*phenyl*-, m.p. 240—242° (from ethyl acetate) (Found: C, 73.0; H, 5.9; N, 4.6. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); 2-*oxo*-9-*phenyl*-, m.p. 244—246° (from ethyl acetate) (Found: C, 73.6; H, 6.0; N, 4.8. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.9; N, 4.7%); 1-*methyl*-2-*oxo*-, m.p. 188—190° (from ethyl acetate) (Found: C, 67.1; H, 6.5; N, 6.0. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%), 1-*benzyl*-2-*oxo*-, m.p. 227—229° (from toluene) (Found: C, 73.5; H, 6.1; N, 4.3. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%); 1-(2,6-*dichlorobenzyl*)-2-*oxo*-, m.p. 226—228° (from ethyl acetate) (Found: C, 60.4; H, 4.6; N, 3.7. $C_{19}H_{17}Cl_2NO_3$ requires C, 60.3; H, 4.5; N, 3.7%).

Rearrangement of 4,5-*Dihydrospiro*{[1]*benzazocin*-6(3H),2′-*oxiran*}-2(1H)-*one* (IVa).—To a solution of the oxiran (1.01 g) in methylene chloride (25 ml) was added boron trifluoride–ether complex (0.27 ml). After 2½ h the solution was diluted with aqueous 10% sodium carbonate and extracted with ethyl acetate (3 × 100 ml). The extracts were washed with brine (2 × 25 ml), dried ($MgSO_4$), and evaporated (0.95 g). Crystallisation of the residue from acetonitrile gave 3,4-dihydrocarbazol-1(2*H*)-one, m.p. 167—169° (lit.,[7] 169°) (0.25 g), identical (n.m.r., i.r., and mass spectroscopy, m.p. and mixed m.p.) with an authentic sample.

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