SYNTHESIS OF 1,2,3,4,5,6-HEXAHYDRO-2,6-METHANO-1-BENZAZOCIN-11-ONES

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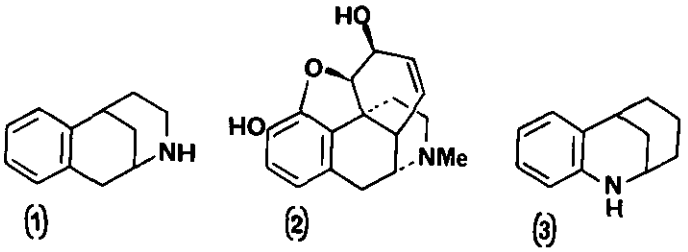
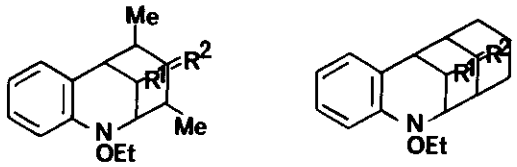
Abstract - 4aH-4a-Methyl-2,3,4-9-tetrahydrocarbazoles can be converted into 1,2,3,4,5,6-hexahydro-2,6-methano-6-methyl-1-benzazocin-11-ones by successive reaction with bromine and aqueous ammonium carbonate.

Interest in the benzomorphans[1] stems from their possible utility as analgesics[2] since the 1,2,3,4,5,6-tetrahydro-2,6-methano-3-benzazocine tricyclic ring system (1) represents three of the five rings of morphine (2). Amongst the very considerable number of synthetic benzomorphan analogues[1,3] which have been described, representatives of all isomers of (1) with the nitrogen at an alternative position in the aliphatic portion had been reported[1] except, until recently[4a], the isomer (3) with nitrogen at position 1, a 1,2,3,4,5,6-hexahydro-2,6-methano-1-benzazocine.

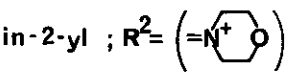


(1) (2) (3)

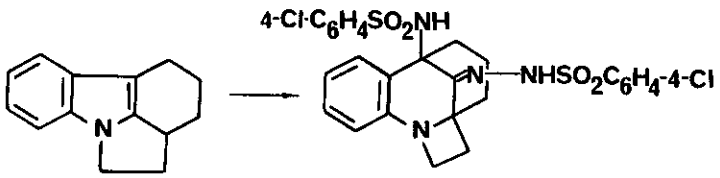
In attempts[4] to introduce substituents into the quinoline 2-position it was found that N-ethoxyquinolinium salts react with ketone enamines in such a way as to add the two ketone α-positions to the quinoline 2- and 4- positions. Thus with the morpholine enamine of pentan-3-one, the tricyclic salt (4) was formed[4a], this being the first and only tricyclic example of a compound with the ring system (3) reported thus far, though more complex ketones reacted to give analogues, (5) from cyclohexanone morpholine enamine for example[4b].



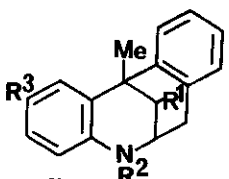
(4) (5)

R^1 = quinolin-2-yl ; R^2 = 

In other work[5] also not specifically designed to produce compounds containing the ring system (3), reaction of the tetracyclic indole (6) with 4-chlorobenzenesulphonyl azide gave, amongst other products, the tetracycle (7). There are several examples[6] of the 6,12-methanodibenz[b,e]azocine system (8) prepared in each case by addition of benzylmagnesium bromide to the 2-position of a quinolinium salt and then strong acid catalysed intramolecular Friedel-Crafts cyclisation - the Grewe cyclisation[1].

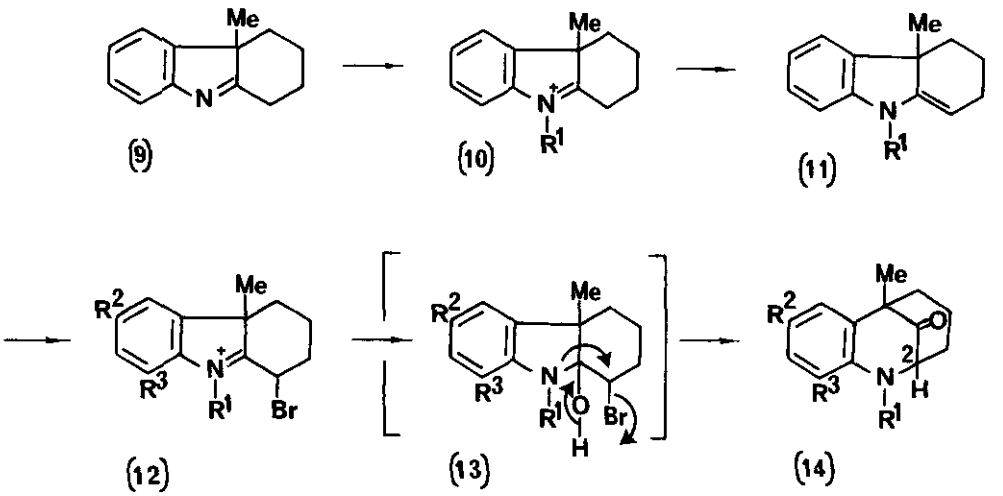


(6) (7)



(8)

We report here an approach to systems containing (3) based upon a 4aH-4a-substituted 1,2,3,4-tetrahydrocarbazole; the simplest member, indolenine (9)[7] was used in these studies. Such compounds are readily produced by the Fischer indole synthesis[8] using the arylhydrazone of a 2-substituted cyclohexanone.



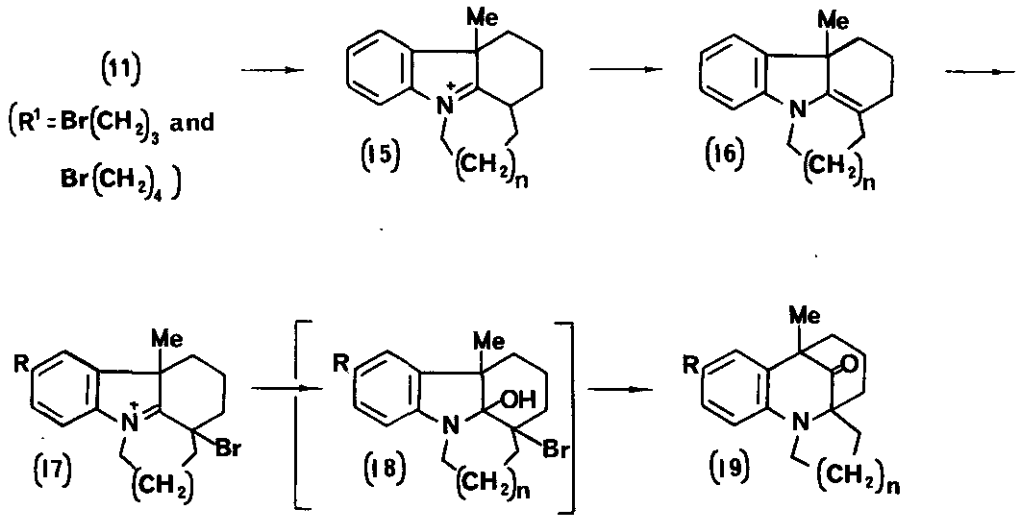
	R^1	R^2	R^3
a	Me	H	H
b	Me	Br	H
c	Me	Br	Br
d	Et	H	H
e	Et	Br	H
f	Et	Br	Br
g	$Br(CH_2)_3$	Br	H
h	$Br(CH_2)_3$	Br	Br
i	$MeO(CH_2)_3$	Br	H
j	$MeO(CH_2)_3$	Br	Br
k	$Br(CH_2)_4$	H	H
l	$Br(CH_2)_4$	Br	Br
m	$MeO(CH_2)_4$	Br	H

Quaternisation of (9) gave salts (10) which were easily and quantitatively converted into the corresponding enamine (11) by treatment with cold aqueous sodium hydroxide. The enamines were unstable and not crystalline and were used without purification for subsequent reaction with bromine. Even at low temperature and with one mol equivalent of the halogen it was impossible to prevent some aromatic ring bromination occurring as well as the desired reaction at the enamine functionality. It was shown that the use of three mol equivalents of bromine produced a mixture containing now principally ring dibrominated material.

The mixture of bromo-immonium salts (12, R^2=R^3=H; R^2=Br, R^3=H; R^2=R^3=Br) produced was reacted with

ethanolic aqueous ammonium carbonate, initially at low temperature and then at room temperature. As in previous work[3a, 9] in the parent benzomorphan series, and recently in model systems[10], this base treatment effected a rearrangement[11] ((12) → (13) → (14))* and produced ketones (14, R^2=R^3= H; R^2=Br, R^3=H; R^2=R^3=Br) which were separated chromatographically. Molecular formulae were established for some of those which were not crystalline by the preparation of a 2,4-dinitrophenylhydrazone and for others by accurate mass measurement of molecular ions.

The ketones were fully characterised spectroscopically (see Table). Of particular relevance to the establishment of the structures of the rearranged ketones were the presence of carbonyl IR stretching bands at ca.1720 cm^{-1} and substantial M-28 (M-CO) peaks in each mass spectrum, the typically aniline and bromo-aniline UV absorptions and one proton triplet signals, at ca. τ 6.3. which correspond to the proton at C-2 in (14). In those ketones carrying two aromatic bromine atoms this signal was at higher field at ca. τ 6.6.



	R	n
a	H	1
b	Br	1
c	H	2

*The rearrangement may procede by cleavage of the C-N bond followed by N displacement of halogen rather than synchronously as implied by the arrows on (13).

In order to further explore the generality of the sequence described above, we examined the salts (10) resulting from quaternisation of (9) with 1,3-dibromopropane and 1,4-dibromobutane. We reasoned that the enamines (11, R^1=Br$(CH_2)_3$ and R^1=Br$(CH_2)_4$) from these salts would alkylate at C-1 intramolecularly generating tetracyclic salts (15, n=1 and 2) and that from the enamines (16) corresponding to these, via intermediates (17) and (18), tetracycles (19) should be available. In the event, such materials were produced, though in disappointingly poor yields, and accompanied by products (14g-j) and (14k-m) in which the intramolecular alkylation had not occurred.

EXPERIMENTAL

General procedure for preparation of ketones (14a , d), bromo-ketones (14b, c) and dibromo-ketones (14c, f) exemplified by preparation of 1,2,3,4,5,6-hexahydro-2,6-methano-1,6-dimethyl-1-benzazocin-11-one (14a), 8-bromo-1,2,3,4,5,6-hexahydro-2,6-methano-1,6-dimethyl-1-benzazocin-11-one (14b), and 8,10-dibromo-1,2,3,4,5,6-hexahydro-2,6-methano-1,6-dimethyl-1-benzazocin-11-one (14c). - The methiodide (10, R^1=Me) (11.5 g) was dissolved in water (100 ml) with warming. To the cooled solution aqueous sodium hydroxide (3M, 60 ml) was added and the enamine (11, R^1=Me) thus formed extracted into ether, and the dried ethereal extract evaporated to give the enamine (11, R^1=Me) as an oil (8 g) which was used without further purification.

The enamine (8 g) in dichloromethane (50 ml) was treated with bromine (2 ml) in dichloromethane (50 ml) dropwise during 0.5 h at -60°C, a yellow precipitate was formed. The mixture was brought to room temperature and the solvent evaporated to leave a mixture of 1-bromo-indoleninium bromides (12a - c) (14.5 g) which was used without purification.

The salts (12a - c) (14.5 g) in 95% ethanol (200 ml) were treated with aqueous ammonium carbonate (4 g in 50 ml) dropwise; a beige precipitate formed. After stirring for 2 h at 70°C and then 24 h at room temperature the alcohol was evaporated and the product extracted with ether as an oil (6.5 g), the components of which were separated by chromatography using silica. A sample (2.5 g) gave, in order of elution, the dibromo-ketone (14c) (31 mg), mp 114-116°C (from methanol), the ketone (14a) (1.0 g) as an oil (DNP derivative, mp 185-188°C (from acetone)), and the monobromo-ketone (14b) (0.35 g), mp 111-113°C (from methanol).

General procedure for preparation of ketones (19a, c) and bromo-ketone (19b) exemplified by preparation of 1H-1,2,3,9,10,11,12,12a-octahydro-9,12a-methano-9-methylpyrrolo[1,2-a] [1]-benzazepin-13-one (19a) and 1H-7-bromo-1,2,3,9,10,11,12,12a-octahydro-9,12a-methano-9-methylpyrrolo [1,2-a] [1]-benzazepin-13-one (19b). - The indolenine (9) (2 g) and 1,3-dibromopropane (4 ml) were heated in refluxing methanol (40 ml) for 36 h. The solvent was evaporated and the residue partitioned between water and ether. The ether-washed aqueous layer was treated with aqueous

sodium hydroxide (3 M, 50 ml) and extracted with ether to give a gum which was heated in refluxing ethanol overnight. Removal of the ethanol and partitioning between water and ether gave organic-soluble material (0.85 g) which was rejected. The aqueous phase was treated with sodium hydroxide (3 M, 50 ml) and extracted with ether to give a gum containing the enamine (16, n=1) (mass spectrometry). Reaction of this enamine in dichloromethane with bromine (0.3 ml) in dichloromethane (20 ml) at -70°C for 0.5 h was followed by evaporation of solvent and treatment of the residue in ethanol (30 ml) with aqueous ammonium carbonate (0.45 g in 30 ml) at -30°C. After 2 h at this temperature the mixture was stirred at 20°C for 24 h. Evaporation of the solvent and addition of water and dichloromethane gave an organic extract which was evaporated to leave an oil (0.53 g). Chromatography over silica gel gave, in order of elution, ketone (19a) (30 mg) as a gum, monobromo-ketone (19b) (126 mg) m p 109-111°C (from methanol), dibromo-methoxy-ketone (14j) (55 mg), monobromo-methoxy-ketone (14i) (69 mg), and 4aH-6-bromo-1,2,3,4-tetrahydro-4a-methyl-carbazole (82 mg) all as gums.

In another attempt to prepare ketone (19a) using the indolenine (9) (5 g) the procedure was modified in substituting a reflux in methanol for 2 h for the overnight reflux in ethanol. No products (19) were obtained but only, after chromatography, in order of elution, tribromo-ketone (14h) (0.78 g) (DNP derivative, mp 201-204°C (from methanol)) as a gum and dibromo-ketone (14 g) (0.73 g) (DNP derivative, mp 188-190°C (from methanol)) also as a gum.

Ketone (19a) had λ_{max} (EtOH) 258 and 302 nm (log ε 3.8 and 3.0); ν_{max} (film) 1715 cm^{-1}; τ($CDCl_3$) 2.86 (1H, d, J 8 Hz, H-8), 2.92 (1H, t, J 8 Hz, H-6), 3.32 (1H, t, J 8 Hz, H-7), 3.54 (1H, d, J 8 Hz, H-5), 6.35 (1H, m), 7.68-8.60 (10H, m) and 8.58 (3H, s, CH_3); m/z 241 (M^+, 33%), 213 (45), 198 (12), 184 (24), and 170 (100) (Found, M by mass spectrometry 241.1460. $C_{16}H_{19}NO$ requires M, 241.1453). Ketone (19b) had λ_{max} 271 and 310 nm (log ε 3.7 and 3.8); ν_{max} (nujol) 1720 cm^{-1}; τ($CDCl_3$) 2.84 (1H, d, J 9 Hz, H-6) 2.89 (1H, s, H-8), 3.68 (1H, d, J 8 Hz, H-5), 6.40 (1H, m), 7.69-8.50 (10H, m), and 8.60 (3H, s, CH_3); m/z 321, 319 (M^+, 28, 27%), 293, 291 (59, 58), 278, 276 (11, 10), 264, 262 (22, 26), and 250, 248 (100, 92) [Found C, 59.9; H, 5.7; N, 4.0; Br, 24.8% $C_{16}H_{18}BrNO$ requires C, 59.8; H, 5.6; N, 4.4; Br, 25.0%]. Ketone (19c) had λ_{max} (EtOH) 260, 304, and 330 nm (log ε 4.3, 3.5, and 3.3); ν_{max} (film) 1720 cm^{-1}; τ($CDCl_3$) 2.90 (1H, t, J 8 Hz, H-7), 2.92 (1H, d, J 8 Hz, H-9), 3.24 (1H, d, J 8 Hz, H-6), 3.32 (1H, t, J 8 Hz, H-8), 6.12 (1H, m), 6.90-8.75 (13H, m), and 8.55 (3H, s, CH_3); m/z 255 (M^+, 8%), 227 (16), 298 (21), and 184 (100) (Found, M by mass spectrometry, 255.1626. $C_{17}H_{21}NO$ requires M, 255.1623).

Table 1,2,3,4,5,6-Hexahydro-2,6-methano-1-benzazocin-11-ones

Compound	Formula	Yield	m p (°C)	c:o(cm^{-1})	λ_{max}(EtOH) (log ε)	τ (CDCl$_3$) CMe	NMe	OMe	H-2	H-7	H-8	H-9	H-10	M$^+$ by M.S. (Calculated)	Analysis (%) (Calculated) C	H	N	Br	DNP derivative m p (°C)	Analysis (%) C	H	N	Br
14a	$C_{14}H_{17}NO$	46[1]	amorphous	1720	258, 304, 330 (4.3, 3.6, 3.2)	8.54	7.50	-	6.30	2.88	3.28	2.84	3.42	215.1306 (215.1310)	-	-	-	-	185-188 (Me_2CO)	60.5 (60.8	5.6 5.3	17.1 17.7)	
14b	$C_{14}H_{16}BrNO$	6[1]	111-113 (MeOH)	1720	267, 310, 335 (4.3, 3.4, 3.3)	8.60	7.10	-	6.32	2.82	-	2.78	3.58	-	-	-	-	-	-	-	-	-	-
14c	$C_{14}H_{15}Br_2NO$	1[1]	114-116 (MeOH)	1725	270, 304 (4.0, 3.6)	8.55	7.22	-	6.70	2.80	-	2.35	-	-	-	-	-	-	-	-	-	-	-
14d	$C_{15}H_{19}NO$	54[1]	amorphous	1730	261, 305, 335 (4.0, 3.0, 2.9)	8.58	-	-	6.30	2.90	3.32	2.84	3.42	229.1470 (229.1467)	-	-	-	-	169-171 (MeOH)	61.3 (61.6	5.6 5.6	17.0 17.0)	
14e	$C_{15}H_{18}BrNO$	9[1]	61-62 (MeOH)	1725	270, 312, 347 (4.2, 3.3, 3.1)	8.60	-	-	6.30	2.86	-	2.75	3.55	-	58.4 (58.3	6.0 5.8	4.4 4.5	25.6 25.9)	195-198 (MeOH)	52.0 (51.5	4.7 4.5	14.7 14.3	16.2 16.6)
14f	$C_{15}H_{17}Br_2NO$	3[1]	amorphous	1720	268, 305 (3.9, 3.5)	8.55	-	-	6.58	2.80	-	2.35	-	386.9654 (386.9658)	-	-	-	-	229-231 (MeOH)	44.3 (44.4	3.7 3.7	11.6 12.4	30.0 28.2)
14g	$C_{16}H_{19}Br_2NO$	7[1]	amorphous	1715	268, 313, 350 (3.9, 3.0, 2.6)	8.60	-	-	6.30	2.87	-	2.80	3.50	402.9755 (402.9795)	-	-	-	-	188-190 (MeOH)	45.6 (45.4	4.0 4.0	11.3 12 0	27.0 28.0)
14h	$C_{16}H_{18}Br_3NO$	6[1]	amorphous	1715	265, 300 (3.8, 3.0)	8.55	-	-	6.63	2.80	-	2.36	-	-	-	-	-	-	201-204 (MeOH)	40.0 (39.9	3.3 3.3	10.3 10.6	36.3 36.3)
14i	$C_{17}H_{22}BrNO_2$	2[2]	amorphous	1720	268, 314, 340 (4.6, 3.7, 3.5)	8.60	-	6.66	6.32	2.85	-	2.78	3.58	353.0834 (353.0815)	-	-	-	-	-	-	-	-	-
14j	$C_{17}H_{21}Br_2NO_2$	1[2]	amorphous	1720	262, 300 (4.6, 4.0)	8.56	-	6.74	6 57	2.84	-	2.39	-	430.9913 (430.9920)	-	-	-	-	-	-	-	-	-
14k	$C_{17}H_{22}BrNO$	1[2]	amorphous	1720		8.32	-	-	6.26	2.78	3.25	2.82	3.34	337.0936 (337.0947)	-	-	-	-	-	-	-	-	-
14l	$C_{17}H_{20}Br_3NO$	2[2]	122-123 (MeOH)	1715	270, 310 (3.0, 2.5)	8.56	-	-	6.60	2.82	-	2.38	-	-	41.4 (41.2	4.1 4.0	2.5 2.8	47.9 48.5)	-	-	-	-	-
14m	$C_{18}H_{24}BrNO_2$	13[2]	amorphous	1720	267, 313, 347 (4.5, 3.6, 3.0)	8.62	-	6.60	6.35	2.74	-	2.85	3.58	367.0978 (367.0971)	-	-	-	-	-	-	-	-	-

Footnotes to Table

1 Yields given are for conditions to minimize aromatic ring bromination.

2 Yields given are for byproducts from formation or attempted formation of tetracycles (19).

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