Cyclialkylation Studies. 3. Acid-Catalyzed Cyclodehydration of Some Benzyltetralols, with and without Rearrangement, To Yield Tetracyclic Hydrocarbons†

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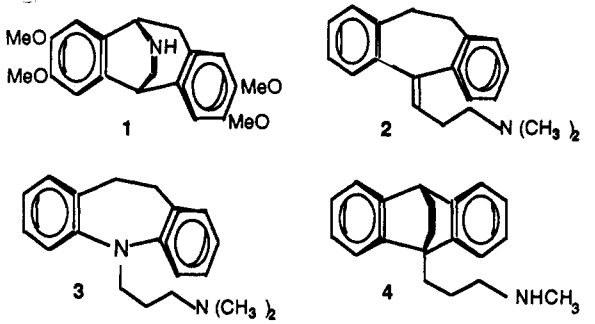
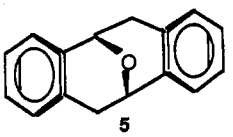
Acid-catalyzed cyclodehydration of some benzyltetralols has been used to prepare tetracyclic hydrocarbons as synthons for compounds of potential pharmacological value. Upon treatment with sulfuric acid at 25 or 40 °C, 4-benzyl-2-tetralol (**15**) gave a 70:30 mixture of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**7**) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**8**). Reaction of **15** with *p*-toluenesulfonic acid in refluxing cyclohexane solution gave the same two products (**7** and **8**) as well as a small amount of 1-benzyl-1,2-dihydronaphthalene (**16**). Treatment of either **15** or **16** with $AlCl_3$ gave only **8**. Treatment of 1-benzyl-2-tetralol (**17**) with $AlCl_3$ also gave **8**. The mechanism of formation of **7** and **8** from **15** and **16** is discussed.

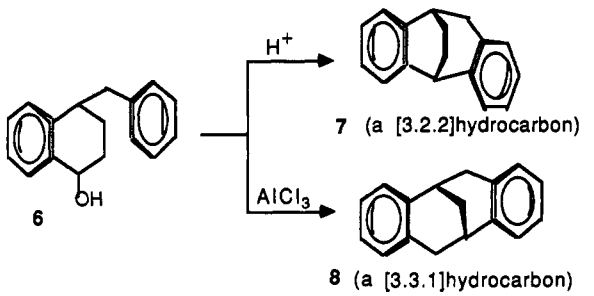
Extensive studies of cyclodehydration and cyclialkylation reactions have been reported,[1,2] but the formation of bridged polycyclic compounds by these processes has not received much attention. A number of pharmacologically active natural products[3] and synthetic analogues[4] contain the 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene system in which nitrogen replaces carbon in one or more positions of the alicyclic structure: i.e., isopavine (**1**[3a,b]) and various related alkaloids.[3c,d] Some synthetic psychoactive compounds contain the simpler but structurally related dibenzocycloheptadiene ring system or an aza analogue: among these are the antidepressant drugs amitriptyline (**2**) and imipramine (**3**). Another antidepressant drug, maprotiline (**4**), contains a different tetracyclic ring system.



Kagan's ether **5** and related molecular clefts (derivatives of Kagan's ether) have a dibenzobicyclo[3.3.1]nonadiene system.[5]



These dibenzobicyclo[3.2.2]- and -[3.3.1]nonadiene systems have been prepared previously by long and tedious synthetic routes.[6,7] During our studies on Friedel–Crafts cyclialkylation reactions, we observed that tetralol **6** gives, on treatment with sulfuric acid, the parent hydrocarbon of the [3.2.2] tetracyclic system (**7**), whereas treatment with $AlCl_3$ gives **8**, the parent hydrocarbon of the [3.3.1] system.[1] This result suggested that access to these dibenzobicyclononadiene systems may now be much simpler and more direct.



A systematic study of new direct synthetic methods for the preparation of dibenzobicyclo[3.3.0]- and -[3.2.1]octadiene and dibenzobicyclo[4.3.0]-, -[3.3.1]- and -[3.2.2]-nonadiene systems has been undertaken. Because of significant biological activities of both natural and synthetic derivatives of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**7**), emphasis was placed on this system, the formation of which has not been readily accessible previously. The critical reaction in the new procedure is an acid-catalyzed intramolecular cyclodehydration of a benzyltetralol.

Benzylcyclohexanol (**9**, $n = 1$, OH at position 1, 2, or 3) and phenylcyclohexylcarbinol (**9**, $n = 1$, OH at the α position) studies[8] indicated that hydride shifts in carbocation intermediates can make the different substrate alcohols equivalent in the cyclodehydration reactions. Similarly, benzylcyclopentanol (**9**, $n = 0$, OH at position 1 or 2) and phenylcyclopentylcarbinol (**9**, $n = 0$, OH at the α position) gave the same product **10**.[9] The presence of

† Part 2: Prasad, R. S.; Roberts, R. M. *Synth. Commun.*, in press.

(1) Low, C.-E.; Roberts, R. M. *J. Org. Chem.* **1973**, *38*, 1909.
(2) (a) Roblin, R. O.; Davidson, D.; Bogert, M. T. *J. Am. Chem. Soc.* **1935**, *57*, 151 and later papers of Bogert et al. (b) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1973**, *38*, 1388 and references cited therein.
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(6) Cioranescu, E. M.; Banciu, M.; Jelescu, R.; Rentzea, M.; Elian, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1969**, *14*, 911.
(7) (a) Roberts, R. M.; Anderson, G. P.; Khalaf, A. A.; Low, C.-E. *J. Org. Chem.* **1971**, *36*, 3342. (b) Stetter, H.; Reischl, A. *Chem. Ber.* **1960**, *93*, 791.
(8) (a) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1936**, 62. (b) Challis, A. A. L.; Clemo, G. R. *Ibid.* **1947**, 1692. (c) Bardhan, J. C.; Banerjee, R. C. *Ibid.* **1956**, 1809. (d) Ghatak, U. R.; Chakravarty, J. *Tetrahedron Lett.* **1966**, 2449. (e) Chakraborti, A. K.; Alam, S. K.; Chakraborti, P. C.; Dasgupta, R.; Chakravarty, J.; Ghatak, U. R.; Kabiraj, A.; Biswas, S. G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1243 and references cited therein.

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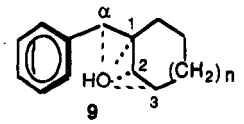

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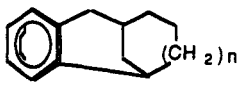

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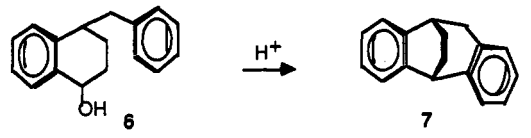
the second aromatic ring in the present systems (benzyltetralols), however, makes for significant differences among substrates with respect to which bicyclic system is favored, since some of the possible intermediate carbocations are benzylic.

It has already been shown[1] that 4-benzyl-1-tetralol (6) gives on cyclodehydration mainly the [3.2.2] bicyclic system 7, whereas substituted benzyltetralols 11 and 13 give the [3.3.1] bicyclic systems 12 and 14, suggesting that the stability of the intermediate carbocation and steric factors are important in determining the nature of the product formed.



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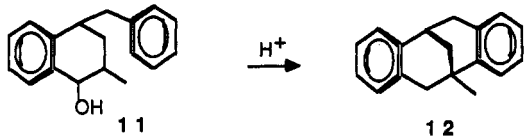

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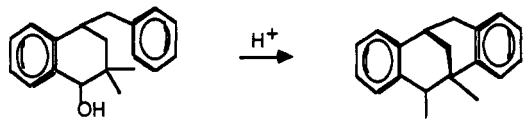
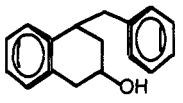


13 14

In continuation of our investigations in this series, we have now chosen to study the behavior of 4-benzyl-2-tetralol (15), 1-benzyl-1,2-dihydronaphthalene (16), and 1-benzyl-2-tetralol (17) upon treatment with acid catalysts.



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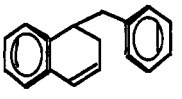

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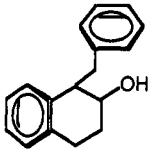

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Treatment of 4-benzyl-2-tetralol (15) with sulfuric acid at room temperature resulted in the formation of two products; the reaction was complete within 20 min as evidenced by the disappearance of the starting material on GC. By comparing the GC and NMR spectra of these products with those of authentic samples, they were identified as 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (7) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (8). They were present in the ratio of 70:30. When the reaction was repeated at varying temperatures from −70 to 80 °C, it was observed that at −70 °C no reaction took place (starting material was recovered), at −25 °C the reaction was slow (even after 8 h only ~10% reaction had taken place), and at −5 to −10 °C the reaction was complete within 30 min (Table I).

For higher temperature studies, *p*-toluenesulfonic acid (PTS) was used as the protonic acid. While at room temperature with sulfuric acid the reaction was complete within 30 min, no reaction took place with PTS. However, on heating 15 to reflux with PTS in cyclohexane solution,

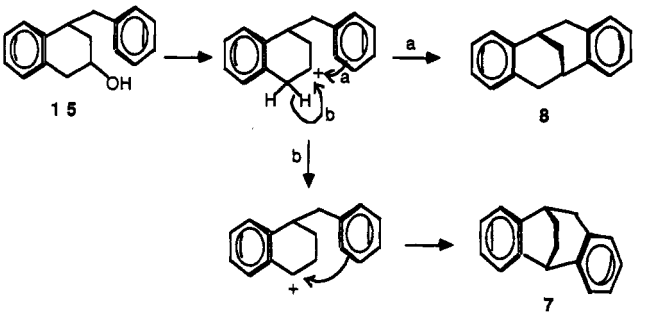
(9) Groves, L. H.; Swan, G. A. *J. Chem. Soc.* **1951**, 871 and references cited therein.

Table I. Reaction of 4-Benzyl-2-tetralol with Sulfuric Acid

temp (°C)	time	7 (%)	8 (%)	15 (%)
40	10 min	70	30	
25	20 min	70	30	
−10	1 h	65	35	
−25	1 h	3	5	90
	4 h	3	5	90
	8 h	3	5	90
−70	8 h	5	5	90

the reaction was complete in 2 h and three products had formed: 10% of dehydrated product (16) and equal amounts of 7 and 8. On continuing the heating, the dehydrated product disappeared in 4 h and only the two products 7 and 8 were left behind in the ratio of 60:40 (Table II).

The formation of these products once again confirms our earlier hypothesis that these cyclodehydration reactions proceed via the formation of stable carbocation intermediates. The initially formed secondary carbocation can directly alkylate the aromatic ring to give the [3.3.1] system 8 or it can rearrange through a 1,2-hydride shift to a more stable secondary *benzylic* carbocation that undergoes cyclization to yield the [3.2.2] system 7. Rearrangement of carbocations is considered to occur for thermodynamic reasons, wherein an initially generated carbocation rearranges to a thermodynamically more stable carbocation.[10]



15 8 7

Interestingly, the 1,2-hydride shift (path b) appears to be faster than direct cyclialkylation as indicated by the product composition. It is also possible that the partitioning of the intermediate cation between two pathways probably depends on the relative transition-state energies for the pathways to 7 to 8.

Whereas the phenylcyclopentyl- (or cyclohexyl-) carbinol and benzylcyclopentanol (or cyclohexanol) gave the same product 10 having the [3.2.1] (or [3.3.1]) system, tetralols gave different products, indicating that the presence of the second aromatic ring makes a significant difference. Further, the cyclialkylation reaction is not going through the intermediate formation of dihydronaphthalene 16. On treatment with sulfuric acid, 16 gives 7 as the sole product, whereas 15 gives a mixture of products 7 and 8.

Reaction of 15 with $AlCl_3$ was comparatively slow; in 4 h the main product was 8 (Table III). It has been estimated that the Friedel–Crafts conjugate acid is $\sim 10^5$ times more acidic than 100% sulfuric acid.[11] We had earlier reported[12] that $AlCl_3$ is so strong a Lewis acid that it "levels off" the intrinsic difference in the ease of abstraction of a secondary and tertiary hydride. It would even slow down the reaction by increasing the lifetime of the intermediate carbocation. The fact that the reaction of 15 with $AlCl_3$

(10) Barrow, C. J.; Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1989**, *54*, 2542.
(11) Olah, G. A. In *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, 1963, Vol. 1, p 880.
(12) Roberts, R. M.; Bantel, K.-H.; Low, C.-E. *J. Org. Chem.* **1973**, *38*, 1303.

Table II. Reaction of 15 and 16 with p-Toluenesulfonic Acid

compd	temp (°C)	time	7 (%)	8 (%)	16 (%)
15	25	no reaction			
	80	2 h	44	43	13
		4 h	60	40	
16	80	30 min	4		95
		2 h	55		44
		4 h	100		

Table III. Reaction of 15, 16, and 17 with $AlCl_3$

compd	time (h)	7 (%)	8 (%)	15 (%)	16 (%)	
15	1	4	18	80		
	2	2	52	40		
	3	2	73	15		
	4	2	75	15		
	6	1	90			
16	1	40	15			28[a]
	3.5		52			44[a]
	6.5		65			22[a]
	24		77			6[a]
17	1.5	3	15			81[b]
	3	8	48			43[b]
	4	7	57			35[b]
	6.5	5	76			10[b]
	9	6	90			2[b]

[a] 1,5-Diphenylpentane. [b] 1-Benzyl-2-tetralol.

at room temperature was comparatively slow and the main product of this reaction was 8 confirms that $AlCl_3$ is a very strong acid,[13] for it is only in this strong Lewis acid medium that a less stable carbocation species can exist to the extent that a thermodynamically more stable compound can form from it. Even in the case of 16, on treatment with $AlCl_3$, the initially formed 7 slowly undergoes isomerization by hydride shift to yield 8. (Our earlier study[1] has shown that the compound 7 on treatment with $AlCl_3$ in CS_2 undergoes isomerization to compound 8.)

When 1-benzyl-2-tetralol (17) was treated with sulfuric acid, neither 7 nor 8 was formed. However on treating with $AlCl_3$, once again a thermodynamically stable product 8, was formed.

Thus, 4-benzyl-2-tetralol (15) on treatment with sulfuric acid at room temperature or PTS at 100 °C gives a mixture of 7 and 8, but when treated with $AlCl_3$ yields only 8. 1-Benzyl-2-tetralol (17), on treatment with $AlCl_3$, also gives 8 as the main product, but with sulfuric acid neither 7 nor 8 is formed. On the other hand, 16 with sulfuric acid gives only 7 and with $AlCl_3$ it gives 8. In sulfuric acid medium, the stability of the intermediate carbocation controls the nature of the final product. In the case of the stronger Friedel–Crafts conjugate acid, the thermodynamic stability of the final product determines the path of the reaction.

(13) The principle is well-documented that a less stable carbocation, i.e., a highly electrophilic species, can survive only if it is in a progressively stronger acidic medium. Thus, carbocations of very short half-life can be made stable in superacid media. See: (a) Olah, G. A. et al., reports appearing in *J. Am. Chem. Soc.* since 1965. (b) Gillespie, R. J.; Peel, T. E. *Adv. Phys. Org. Chem.* **1971**, *9*, 1.

Experimental Section[14]

4-Benzyl-2-tetralone (15) and 1-benzyl-1,2-dihydronaphthalene (16) were prepared as described previously.[15] 1-Benzyl-2-tetralol (17) was prepared by a known procedure.[16]

Synthesis of Benzyl-2-tetralols. To an ice-cold stirred suspension of lithium aluminum hydride (2.5 g, 0.06 mol) in dry tetrahydrofuran (60 mL) was added dropwise the solution of tetralone (0.02 mol) in tetrahydrofuran (75 mL) under nitrogen atmosphere. The resulting mixture was refluxed for 3 h and stirred at room temperature for 20 h. Then, it was cooled in an ice bath and decomposed by adding water (30 mL) followed by dilute sulfuric acid (10%, 90 mL). The mixture was extracted with ether. The organic extract was washed with water, dried (anhydrous Na_2SO_4) and concentrated to get the corresponding alcohols.

1-Benzyl-2-tetralol (17) had mp 107–110 °C (hexane): IR (Nujol) 3350, 1450, 1335, 1040 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.94 (s, 1, OH), 1.95–2.15 (m, 2, CH_2), 2.85–3.40 (m, 5, benzylic CH_2 and CH), 4.10–4.20 (m, 1, OCH), and 6.95–7.60 (m, 9, aromatic); mass spectrum m/e (relative intensity) 220 (58), 130 (13), 129 (100), 128 (55), 127 (11), 115 (11), and 91 (31).

4-Benzyl-2-tetralol (15) was a mixture of cis and trans isomers present in the ratio of 1:3.5 as indicated by NMR: IR (neat) 3340, 1480, 1440, 1120, 1060, and 1040 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.70–1.88 (bs, 1, OH), 1.90–2.40 (m, 2, CH_2), 2.60–3.60 (m, 5, benzylic CH_2 and CH), 3.90–4.40 (2m, 1, OCH), 7.00–7.60 (m, 9, aromatic); mass spectrum m/e (relative intensity) 220 (16), 147 (11), 130 (11), 129 (100), 128 (77), 127 (14), 117 (10), 115 (8), 91 (21), and 84 (18).

General Procedure for Cyclodehydration Reaction with Concentrated Sulfuric Acid. In a 25-mL flask was placed 1 mL of concd sulfuric acid (93% by weight) and 6 mL of dichloromethane. The solution of benzyltetralol (200 mg) in dichloromethane (6 mL) was added slowly with stirring at various temperatures. At various time intervals, an aliquot was withdrawn with a pipet and decomposed at once in a small vial containing ice, then extracted with ether, and analyzed by GLPC. The identification of the products was accomplished by comparing their chromatographic behavior and NMR spectra with those of the authentic samples.

Treatment of 15 and 16 with p-Toluenesulfonic Acid. The substrate (15 or 16, 8 mmol) was dissolved in cyclohexane (15 mL) and refluxed with p-toluenesulfonic acid (200 mg) with azeotropic removal of water. At various time intervals, an aliquot was withdrawn with a pipet, decomposed with water, and extracted with ether. It was then analyzed by GLPC.

General Procedure for Reaction with Aluminum Chloride. The substrate (10 mmol) was dissolved in carbon disulfide (15 mL), and to this was added aluminum chloride (15 mmol). The reaction mixture was stirred at room temperature. An aliquot was withdrawn at various time intervals, decomposed with ice–water, and extracted with ether. This was then analyzed by GLPC.

Acknowledgment. Support for this work by the Robert A. Welch Foundation is gratefully acknowledged.

(14) All temperatures were uncorrected. The IR spectra were recorded on a Beckman Acculab-8 instrument. The NMR spectra were recorded on Varian EM-390 and QE 300 instruments. Mass spectra were recorded on Dupont 21-491 instrument and high-resolution mass spectra were recorded on VG ZAB 2E instrument. GLC was performed with a Hewlett-Packard gas chromatograph, Model 5890, equipped with a flame ionization detector using helium as a carrier gas and BP-1 capillary column (25 m).

(15) Prasad, R. S.; Roberts, R. M. *Synth. Commun.*, in press.

(16) Berney, D.; Schuh, K. *Helv. Chim. Acta* **1976**, *59*, 2059.