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The synthesis of 5-aminomethyl-5-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene derivatives **3** was accomplished by two separate routes. The first route involves the reaction of **4** with Corey's Reagent followed by reaction with either amines or hydrazines. The reaction products with hydrazines (*e.g.* **6**) were hydrogenolyzed, either with hydrogen in the presence of platinum, or with hydrazine in the presence of Raney nickel to yield **3**. The second route to these compounds (**3**) proceeds by a Reformatsky reaction on **4** followed by acid-hydrazide formation and Curtius degradation of **8** to afford spirooxazolidones **9**. Compounds **9** can be alkylated on nitrogen (**10**), and either **9** or **10** hydrolyzed to give the target compounds **3**.

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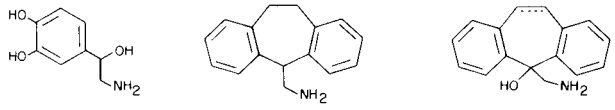
Norepinephrine (**1**) and a number of synthetic sympathomimetric amines bear the α-hydroxy-β-aminoethyl side chain. Compounds possessing a dibenzocycloheptene moiety (1-3) often exhibit an interesting spectrum of biological activities.



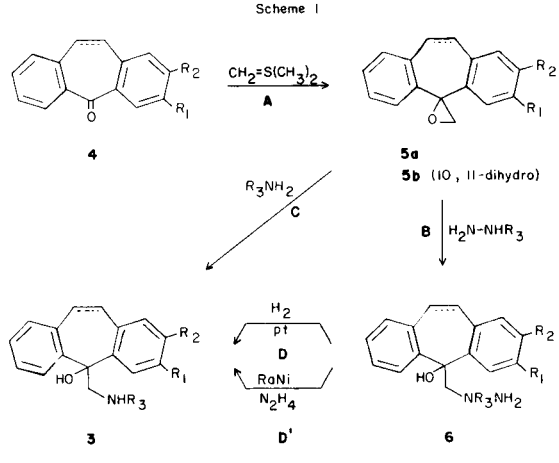
1 2 3

It appeared of interest of us to combine the two functionalities and prepare compounds in which the aminoalcohol moiety is integrated into the dibenzo[*a,d*]cycloheptene system (Formula **3**) and to investigate their pharmacological profile.

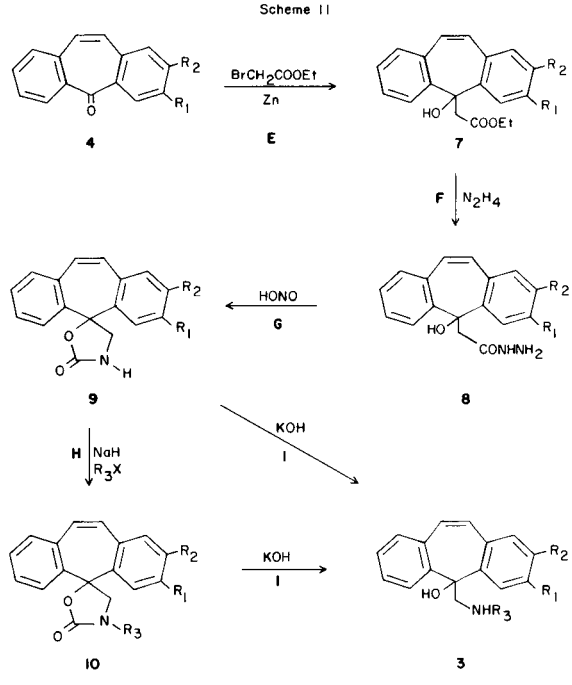
Compounds of formula **2** have been prepared (4,5) and the *N,N*-disubstituted derivative of **3** has been reported (6). However, the reported synthetic procedures are not applicable to the preparation of **3**.

In our laboratory, two synthetic approaches were developed to prepare the target compounds of type **3** (see Schemes I and II).

Scheme I



Scheme II



In Scheme I, the intermediate epoxides **5** were readily prepared from the reaction of dibenzo[*a,d*]cycloheptane derivatives (**4**) with dimethylsulfonium methylide according to the procedure described by Corey (7,8). Davis and co-workers (3) reported the preparation of **5a** (R_1, R_2 = H) using Corey's procedure, but claimed that the corresponding 10,11-dihydro analog **5b** cannot be prepared by this method. In agreement with a report by Ackermann and coworkers (9) we found that this compound can analogously be synthesized by Corey's method in high yield.

Some of the epoxides in this series of compounds were however rather unstable in the reaction medium (DMSO) and tended to decompose partially during the work-up process. In most of the cases, the crude epoxides **5** were therefore directly reacted with hydrazine and the resulting hydrazino alcohols **6** were characterized.

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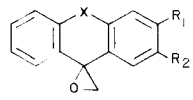
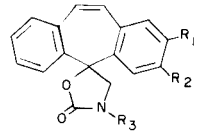
Table I



Compound No.	X	R_1	R_2	Yield, %	M.p. °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. C	(Found) H
5a	CH=CH	H	H	91	91-93		$C_{16}H_{12}O$	Lit., Ref. 3	
5b	CH_2CH_2	H	H	85	77-78		$C_{16}H_{14}O$	Lit., Ref. 9	
5c	CH=CH	H	Cl	(a)					
5d	CH=CH	OCH_3	OCH_3	(a)					
5e	CH_2CH_2	OCH_3	OCH_3	88	85-88	ether/pentene	$C_{18}H_{18}O_3$	76.6 (76.9)	6.4 (6.4)

(a) The material was carried on to the next step without further purification.

Table 2

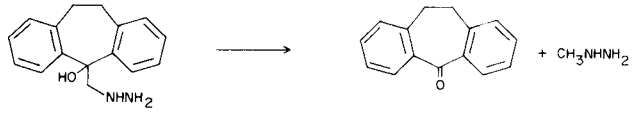


Compound No.	R_1	R_2	R_3	Yield, %	Procedure	M.p. °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. C	H	N	(Found) Cl
9a	H	H	H	78	G	305-306	ethanol	$C_{17}H_{13}NO_2$	77.6	5.0	5.3	
									(77.9	5.1	5.6)	
9b	H	Cl	H	95	G	253-256	benzene	$C_{17}H_{12}ClNO_2$	68.6	4.1	4.7	
									(68.8	4.3	4.3)	
9c	OCH_3	OCH_3	H	100	G	237-240	benzene	$C_{19}H_{17}NO_4$	70.6	5.3	4.3	
									(70.8	5.4	4.4)	
10a	H	H	CH_3	91	H	168-171	ether	$C_{18}H_{15}NO_2$	78.0	5.5	5.1	
									(77.6	5.3	4.8)	
10b	H	Cl	CH_3	100	H	149-152	ether/pentane	$C_{18}H_{14}ClNO_2$	69.3	4.5	4.5	11.4
									(69.1	4.3	4.7	11.5)
10c	H	Cl	$CH(CH_3)_2$	50	H	157-160	ether/pentane	$C_{20}H_{18}ClNO_2$	70.7	5.3	4.1	10.4
									(70.8	5.3	4.0	10.8)

Compounds of type **6** (where R_3 = H), upon catalytic hydrogenation at atmospheric pressure in the presence of platinum oxide, furnished the desired compounds **3** in good yields without concomitant reduction of the 10,11-double bond. Cleavage of the N-N bond was also accomplished by treating **6** with hydrazine hydrate in the presence of Raney Nickel catalyst at 60°.

Although aminoalcohols **3** were alternately obtained from epoxides **5** by reaction with amines at 120° in a steel vessel, this procedure did not consistently result in high yields and is not conducive for large scale preparation.

It is interesting to note that when compound **6a** was heated neat to 200° or refluxed in chlorobenzene for 24 hours, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one was isolated, accompanied by methylhydrazine. This same fragmentation was observed in the mass spectrometer (70 eV, source 290°).

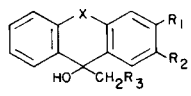


6a

The second approach for the preparation of **3** (Scheme II) involves the synthesis of spirooxazolidone **9** which may be formed by a Curtius rearrangement of a β-hydroxy acid azide, derived from hydrazide **8**. Transformations of this nature were first reported by Schroeter (10) and then by several other workers (11-15).

Compounds of type **7** were readily prepared by a Reformatsky reaction of **4** with ethyl bromoacetate (Table 3). Treatment of **7** with anhydrous hydrazine at 80-85° furnished **8** in excellent yields (Table 3). Subsequent treatment of hydrazide **8** with sodium nitrite in cold aqueous acetic acid produced **9** in nearly quantitative yield (Table

Table 3



Compound No.	X	R_1	R_2	R_3	Yield, %	Procedure	M.p. °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. C	H	N	(Found) Cl
3a	CH_2CH_2	H	H	NH_2	85	D	147-149	ether	$C_{16}H_{17}NO$	80.3	7.2	5.9	
					25	C				(80.4	7.1	5.9)	
3b	CH_2CH_2	OCH_3	OCH_3	$NHCH_3$	11	C	177-178 (a)	ethanol/ether	$C_{23}H_{27}NO_7$	64.3	6.3	3.3	
										(64.4	6.5	3.2)	
3c	CH=CH	H	H	NH_2	46	D	117-120	ether	$C_{16}H_{15}NO$	81.0	6.4	5.9	
					67	C				(81.1	6.4	5.8)	
					73	I							
					75	D'							
3d	CH=CH	H	Cl	NH_2	38	I	88-91	ether/pentane	$C_{16}H_{14}ClNO$	70.7	5.2	5.2	13.0
					4	D				(71.0	5.4	5.0	13.0)
3e	CH=CH	OCH_3	OCH_3	NH_2	70	I	128-130	ether/pentane	$C_{18}H_{19}NO_3$	72.7	6.4	4.7	
					2.5	D				(72.6	6.6	4.6)	
3f	CH=CH	H	H	$NHCH_3$	81	I	114-116	ether/pentane	$C_{17}H_{17}NO$	81.2	6.8	5.6	
										(81.0	7.1	5.3)	
3g	CH=CH	H	Cl	$NHCH_3$	87	I	164-167 (a)	ethanol/ether	$C_{21}H_{20}ClNO_5$	62.8	5.0	3.5	8.8
										(62.5	5.2	3.2	8.6)
3h	CH_2CH_2	OCH_3	OCH_3	$NHCH_3$	11	C	177-178 (a)	ether	$C_{23}H_{27}NO_7$	64.3	6.3	3.3	
										(64.4	6.5	3.2)	
3i	CH=CH	H	H	$NHCH(CH_3)_2$	71	C	75-78	ether	$C_{19}H_{21}NO$	81.7	7.6	5.0	
										(82.0	7.5	5.0)	
3j	CH=CH	H	Cl	$NHCH(CH_3)_2$	72	I	185-187 (a)	ethanol/ether	$C_{23}H_{24}ClNO_5$	64.2	5.6	3.3	8.2
										(64.1	5.7	3.1	8.5)
6a	CH_2CH_2	H	H	$NHNH_2$	85	B	98-102	ether	$C_{16}H_{18}N_2O$	no analysis (b)			
6b	CH_2CH_2	H	H	$N(CH_3)NH_2$	42	B	138-140	ether	$C_{17}H_{20}N_2O$	76.1	7.5	10.4	
										(75.9	7.7	10.5)	
6c	CH=CH	H	H	$NHNH_2$	78	B	129-132	methanol	$C_{16}H_{16}N_2O$	76.2	6.4	11.1	
										(76.4	6.7	11.2)	
6d	CH=CH	H	Cl	$NHNH_2$	64	B	119-122	ether	$C_{16}H_{15}ClN_2O$	67.0	5.3	9.8	
										(67.2	5.4	9.7)	
6e	CH=CH	OCH_3	OCH_3	$NHNH_2$	70	B	184-187	methanol	$C_{18}H_{20}N_2O_3$	69.2	6.5	9.0	
										(68.9	6.6	8.8)	
7a	CH=CH	H	H	COOEt	82	E	102-103	ether		literature reference 16			
7b	CH=CH	H	Cl	COOEt	86	E	102-104	ether/pentane	$C_{19}H_{17}ClO_3$	69.4	5.2		10.8
										(69.4	5.2		11.1)
7c	CH=CH	OCH_3	OCH_3	COOEt	72	E	140-143	ethyl acetate	$C_{21}H_{22}O_5$	71.2	6.3		
										(71.1	6.3)		
8a	CH=CH	H	H	$CONHNH_2$	84	F	192-194	ethanol	$C_{17}H_{16}N_2O_2$	72.8	5.8	10.0	
										(72.9	6.1	10.1)	
8b	CH=CH	H	Cl	$CONHNH_2$	87	F	190-193	ethanol	$C_{17}H_{15}ClN_2O_2$	64.9	4.8	18.9	11.3
										(64.7	4.8	19.2	11.0)
8c	CH=CH	OCH_3	OCH_3	$CONHNH_2$	77	F	217-219	ethanol	$C_{19}H_{20}N_2O_4$	67.0	5.9	8.2	
										(67.4	5.4	8.3)	

(a) Maleic acid salt. (b) Material used in next step without further purification.

2). These spirooxazolidones can easily be alkylated on nitrogen in high yield by initial formation of the sodium salt with sodium hydride followed by reaction with an alkyl iodide. As expected, secondary alkyl iodides (*e.g.* isopropyl iodide) do not alkylate in as high yields as primary alkyl iodides. Standard hydrolysis of either **9** or **10** with ethanolic potassium hydroxide allowed the isolation of the desired aminoalcohols **3** in good yields (Table 3).

Compound **5a** in the nmr (deuteriochloroform) exhibits a singlet at δ 7.0, which is attributed to the two olefinic protons, and a singlet at δ 2.65 which are the two methylene protons in the oxirane. The dihydro compounds **5b** and **5c** exhibit a multiplet between δ 3.6-2.6 for the two methylenes, while the epoxide methylene singlet moves downfield to δ 2.95.

In virtually all the compounds, the olefinic or methylene signals in the 7-membered ring behave spectrally as indicated above. The methylene adjacent to the ester in **7** appears as a doublet at δ 2.95 (deuteriochloroform), while in the hydrazide **8** it is observed as a singlet between δ 2.8 and 2.65 (DMSO-d_6). The typical signals observed for the methylenes adjacent to the amine functionalities in the remainder of the compounds (deuteriochloroform) are as follows: compounds **6**, singlet between δ 3.35-3.2; compounds **9**, singlet between δ 3.75-3.7; compounds **10**, singlet at δ 3.6; compounds **3**, multiplet between δ 3.2-3.0.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

The starting 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones and their 10,11-dihydro analogs (**4**) were prepared according to previously published procedures (17).

Synthesis of Spiroepoxides (**5**) (Table 1).

Procedure A.

Under a blanket of nitrogen, 45 ml. of anhydrous dimethylsulfoxide was added to 0.04 mole of sodium hydride (57% in mineral oil, pentane washed) and the mixture was stirred at 70° for 45 minutes. Tetrahydrofuran (45 ml.) was added and the solution was cooled to 0°. To this solution was added dropwise a solution of trimethylsulfonium iodide (0.036 mole) in 45 ml. of dimethylsulfoxide plus 15 ml. of tetrahydrofuran, keeping the temperature of the reaction below 5°. Next, a solution of 0.02 mole of **4** in 15 ml. of tetrahydrofuran was added dropwise and the resulting mixture was stirred at 0° for 30 minutes and then at room temperature for 1 hour. The mixture was poured into 400 ml. of cold water and the precipitate extracted into pentane. The organic phase was washed well with water and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the product.

Reaction of **5** with Hydrazines (Table 3).

Procedure B.

A mixture of 0.01 mole of **5** in 25 ml. of the anhydrous hydrazine was refluxed for 2 hours. The mixture was poured into 200 ml. of cold water. The resulting precipitate was filtered, washed well with water and dried. The product was then recrystallized from an appropriate solvent (see Table 3).

Formation of **3** by Reaction of **5** with Amines (Table 3).

Procedure C.

A mixture of 0.02 mole of **5** in 30 ml. of the amine was heated in a steel vessel at 120° for 24 hours. After cooling, the amine was allowed to evaporate. The resulting solid was dissolved in aqueous 0.5*M* citric acid and the solution was washed with ether. The aqueous phase was basified with 25% sodium hydroxide and the mixture was extracted into ether. After drying over sodium sulfate the solvent was removed under reduced pressure to furnish the product. If the product was not crystalline, it was isolated as the maleic acid salt.

Formation of **3** by Catalytic Reduction of **6** (Table 3).

Procedure D.

A solution of 0.03 mole of **6** in 150 ml. of ethyl acetate and 40 ml. of acetic acid was hydrogenated at one atmosphere, in the presence of 0.5 g. of platinum oxide, for 8 hours. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The resulting oil was neutralized with 10% sodium bicarbonate and the mixture extracted into methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure to furnish the product.

Reduction of **6** with Hydrazine Hydrate.

Procedure D'.

To a solution of 0.4 mole of **6** in 1000 ml. of methanol 150 ml. of hydrazine hydrate was added. The mixture was heated to 40° and then 50 g. of Raney nickel catalyst was added in small portions (foaming occurs). After stirring at 60° for 15 minutes the mixture was cooled to room temperature and the catalyst was filtered through celite. The solvent was removed from the filtrate under reduced pressure and the residue was dissolved in methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure to furnish the product.

Synthesis of **7** by the Reformatsky Reaction (Table 3).

Procedure E.

To a suspension of 10 g. of zinc (10 mesh) in 120 ml. of benzene was added a solution of 0.038 mole of **4** and 0.05 mole of ethyl bromoacetate in 75 ml. of benzene dropwise. When 25% of the solution was added, the mixture was heated slightly to allow the reaction to commence. The remainder of the solution was added at such a rate as to keep a gentle reflux. After addition, the mixture was refluxed for 4 hours. The mixture was poured into 20% aqueous acetic acid and was extracted into ethyl acetate. The organic phase was washed with water and after drying over sodium sulfate, the solvent was removed under reduced pressure to furnish the product.

Synthesis of Hydrazides **8** (Table 3).

Procedure F.

A suspension of 0.025 mole of **7** in 80 ml. of anhydrous hydrazine was heated at 80-85° for 5 hours. The hydrazine was removed under reduced pressure and the product was recrystallized from an appropriate solvent (Table 3).

Formation of **9** by a Curtius Reaction of **8** (Table 2).

Procedure G.

To a mixture of 0.045 mole of **8** in 100 ml. of acetic acid, 30 ml. of water, and 45 g. of ice a solution of 10 g. of sodium nitrite in 15 ml. of water was added. The resulting mixture was shaken for 10 minutes, after which time more ice was added and shaking was continued an additional 10 minutes. The mixture was poured into cold benzene and the organic layer was separated and washed with cold water then cold 2*N* sodium carbonate. After drying over sodium sulfate the solvent was removed to furnish the product.

Alkylation of Spirooxazolidones **9** (Table 2).

Procedure H.

To a suspension of 0.01 mole of **9** in 45 ml. of dimethylacetamide 0.01 mole of sodium hydride (50% in mineral oil, pentane washed) was added. After stirring at room temperature for 2.5 hours, 2.5 ml. of the alkyl iodide was added and stirring was continued for an additional 3 hours. The mixture was poured into cold water and the resulting precipitate was filtered, washed with water, and dried to furnish the product.

Hydrolysis of Spirooxazolidones **9** and **10** (Table 3).

Procedure I.

A mixture of 0.01 mole of **9** or **10** and 6 g. of potassium hydroxide in 100 ml. of 95% ethanol was refluxed for 24 hours. The solvent was removed under reduced pressure and to the residue was added 2*N* hydrochloric acid. The solution was washed with ether then the aqueous phase was basified with 2*N* sodium hydroxide. The mixture was extracted into methylene chloride, washed with water, and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the product.

Acknowledgement.

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