

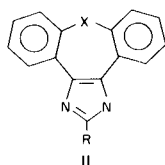
## Synthesis of Some Novel Tetracyclic Imidazole Derivatives

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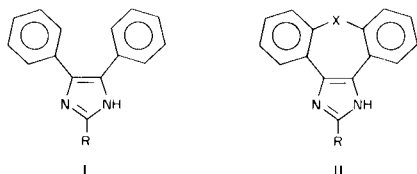
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Representatives have been made of three new heterocyclic systems (II) containing an imidazole ring. Synthetic routes are described for compounds of type II where X = CH<sub>2</sub> (8*II*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]imidazoles), and X = CH<sub>2</sub>CH<sub>2</sub> (8,9-dihydrodibenzo[3,4:7,8]cyclooct[1,2-*d*]imidazoles) and X = S (dibenzo[2,3:6,7]thiepin[4,5-*d*]imidazoles). In addition, improved syntheses are presented for some previously known compounds employed as intermediates in this work.

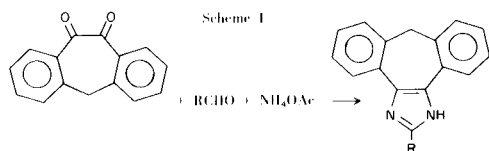


In another connection it became of interest to prepare analogs of some antiinflammatory 2-substituted-4,5-diaryl-imidazoles (I) (I) in which the aromatic rings are connected through a "bridging" group (II). The present work



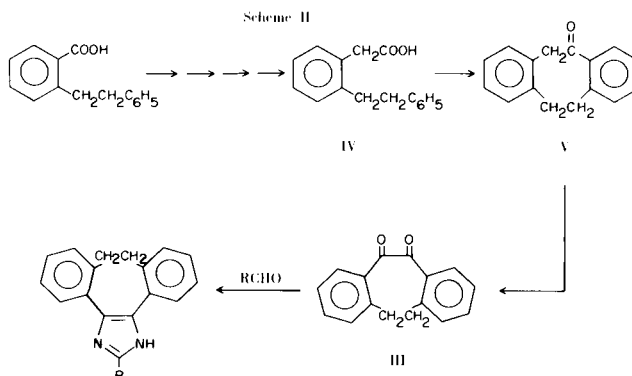
describes the synthesis of representatives in which X = CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, and S. In the following discussion, Roman numerals will be assigned to intermediate compounds and Arabic numerals to final products.

8*II*-Dibenzo[3,4:6,7]cyclohept[1,2-*d*]imidazoles (II, X = CH<sub>2</sub>) were prepared from the known diketone dibenzo[*a,d*]cyclohepta[1,4]diene-10,11-dione (2), ammonium acetate, and the requisite aldehydes by the general imidazole synthesis of Davidson, *et al.* (3) (Scheme 1).



The procedure is illustrated in the Experimental Section for compound 1 and compounds of this type are summarized in Table I.

8,9-Dihydrodibenzo[3,4:7,8]cyclooct[1,2-*d*]imidazoles (II, X = CH<sub>2</sub>CH<sub>2</sub>) were made from 5,6,11,12-tetra-

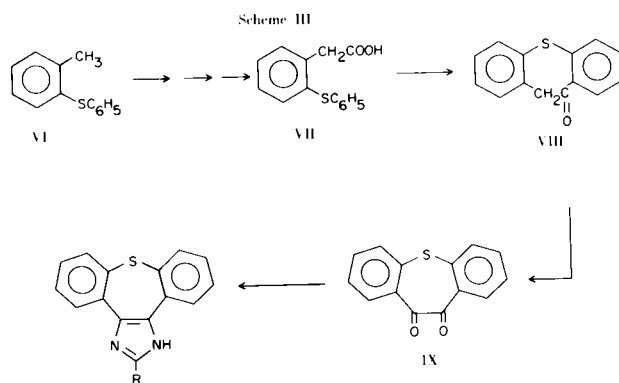


hydrodibenzo[*a,e*]cyclooctene-5,6-dione (2) (III) (Scheme 2). The diketone III was prepared essentially by the method of Leonard *et al.* (2) with two important exceptions: a) the requisite intermediate 2-(2-phenethyl)phenylacetic acid (IV) was prepared by an improved technique (4) and b) the α-diketone III was prepared in good yield from the monoketone V by employing selenium dioxide (see Experimental Section).

The tetracyclic imidazoles were made from diketone III by the method illustrated in the Experimental Section for compound 14. All compounds in Table II were prepared in this general manner except as noted in footnotes to the Table.

Dibenzo[2,3:6,7]thiepin[4,5-*d*]imidazoles (II, X = S) were prepared from the α-diketone 10,11-dihydrodibenzo[*b,f*]thiepin-10,11-dione (IX) which was obtained from the known (5) monoketone VIII (Scheme 3). In our hands, the latter compound was more readily prepared by cyclization of the acid VII using hydrofluoric acid (see Experimental Section) rather than using polyphosphoric acid (5).

The imidazoles were prepared from IX by the method illustrated for compound 22 in the Experimental Section.



### EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were determined in potassium bromide pellets and mass spectra were measured on a Hitachi Perkin-Elmer Model RMU-6E. Analyses were carried out by the Physical Measurements Laboratory of Pfizer, Inc.

Trifluoroacetaldehyde ethyl hemiacetal used for preparing compounds **19** and **26** was purchased from Pierce Chemical Co. and 4-methylthiobenzaldehyde was prepared from 4-chlorobenzaldehyde and methanethiol by the method of Gregory and Kreuchunas (6). All other aldehydes were commercially available and used as received.

2-(*p*-Methoxyphenyl)-8*H*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]imidazole (**1**).

A suspension of 1.6 g. (0.007 mole) of dibenzo[*a,d*]cyclohepta[1,4]diene-10,11-dione (**2**), 4.3 g. (0.056 mole) of ammonium acetate and 2.6 g. (0.019 mole) of *p*-anisaldehyde in 35 ml. of acetic acid was heated to reflux. After 1½ hours, the yellow suspension was cooled, basified with ammonium hydroxide and then diluted with two volumes of water. The supernatant was decanted away from the resulting gum and the gum recrystallized directly from ethanol. After filtration, there was obtained 1.9 g. (80%) of yellow **1**, as the ethanol solvate, m.p. 234-236°. See Table I for analytical data and for related analogs. Most of these compounds formed tenacious solvates even after drying at 100° under high vacuum over phosphorous pentoxide. Mass spectral data and infrared spectra supported the assigned structure in each case.

2-Trifluoromethyl-8*H*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]imidazole (**4**).

A suspension of 1.9 g. (0.0085 mole) of dibenzo[*a,d*]cyclohepta[1,4]diene-10,11-dione (**2**), 1.7 g. (0.0085 mole) of trifluoroacetaldehyde hydrate (Pierce Chem. Co.), and 10 g. of ammonium acetate in 75 ml. of acetic acid was refluxed for 5 hours. Thin-layer chromatographic monitoring (Eastman Chromagram K301R plates, using benzene-5% acetic acid as eluent) indicated two new materials, one more polar and one less polar than the starting diketone (*R<sub>f</sub>* 0.6). An additional 24 hours of reflux did little to change the tlc picture. The reaction was diluted with 150 ml. of water, neutralized with ammonium hydroxide and the resulting yellow solid filtered. This solid mixture (tlc evidence) was triturated with warm 3*N* hydrochloric acid and the insoluble material collected. Recrystallization from 2-propanol yielded 0.47 g. (2%) of 2-trifluoromethyl-8*H*-dihydro-

[3,4:6,7]cyclohept[1,2-*d*]oxazole, m.p. 119-123°. An infrared spectrum exhibited no absorptions near the 3.0 μ (NH) region. Mass spectrum: *m/e* 301 (calcd. 301), 282, 252, 232, 203, 175. This compound is the less polar tlc spot from the reaction.

*Anal.* Calcd. for C<sub>17</sub>H<sub>10</sub>F<sub>3</sub>NO: C, 67.77; H, 3.35; N, 4.65. Found: C, 68.01; H, 3.35; N, 4.64.

The 3*N* hydrochloric acid filtrate from above, containing the more polar tlc spot, was extracted with chloroform, the extracts evaporated and the resulting solid redissolved in 3*N* hydrochloric acid. Adjusting the pH to 6 caused precipitation of a pink solid, which on slow recrystallization from 2-propanol-water gave an amorphous solid. Recrystallization from benzene-hexane yielded an impure solid which was passed through a chromatographic column (Silica Gel G, using methylene chloride eluent) to yield, in fractions 2 and 3, 94 mg. (0.3%) of the pure imidazole **4**, m.p. 238-240°; mass spectrum: *m/e* 300 (calcd. 300).

8,9-Dihydro-2-(*p*-chlorophenyl)dibenzo[3,4:7,8]cyclooct[1,2-*d*]imidazole (**14**).

To a suspension of 4.0 g. (0.017 mole) of the diketone III and 8.09 g. of ammonium acetate in 75 ml. of acetic acid was slowly added a solution of 2.8 g. (0.020 mole) of *p*-chlorobenzaldehyde in 25 ml. of acetic acid. After 1½ hours at reflux, the red reaction mixture was poured into 600 ml. of water and neutralized with ammonium hydroxide. The resulting precipitate was filtered and recrystallized from ethanol to yield 3.4 g. (56%) of **14**, m.p. 347-348°. See Table II for analytical data and for related analogs.

2-(4-Bromophenyl)dibenzo[2,3:6,7]thiepin[4,5-*d*]imidazole Hydrochloride (**22**).

A suspension of 0.60 g. (0.0025 mole) of the diketone IX, 0.46 g. (0.0025 mole) of *p*-bromobenzaldehyde, and 4.0 g. of ammonium acetate in 50 ml. of acetic acid was refluxed for 3 hours. The red reaction mixture was poured into 100 ml. of water, basified with ammonium hydroxide and the resulting yellow precipitate filtered. This solid was dissolved in hot 2-propanol and some 3*N* hydrochloric acid added which caused precipitation of a yellow solid, collected in two crops: 0.62 g. (56%), m.p. 334° dec. See Table III for analytical data and for related analogs.

Intermediates.

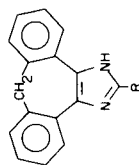
5,6,11,12-Tetrahydrodibenzo[*a,e*]cyclooctene-5,6-dione (III).

To 55 mg. of selenium dioxide suspended in 20 ml. of glacial acetic acid at 80° was slowly added a solution of 100 mg. (0.00045 mole) of 11,12-dihydrocycloocta[*a,e*]dibenzen-5(6*H*)one (**2**) in 5 ml. of acetic acid. After heating at 110° for one hour, the green suspension was cooled, filtered, and the filtrate added slowly to 200 ml. of ice-water. Multiple extractions with ethyl acetate yielded, after drying and evaporating the extracts, a white semi-solid. Trituration with hexane gave 59 mg. (50%) of III, m.p. 127-131° (lit. (2) m.p. 131-132°). Mass spectral (*M<sup>+</sup>* 236) and infrared spectral data supported the structure assigned to III.

10,11-Dihydrodibenzo[*b,f*]thiepin-10-one (VIII).

Approximately 10 ml. of liquid hydrofluoric acid was collected at 0° in a polyethylene bottle. To this acid was added 0.50 g. (0.021 mole) of 2-(phenylthio)phenylacetic acid (**5**). After 2 hours at 0°, the reaction was allowed to stir at room temperature overnight as the HF slowly evaporated. The residue was diluted with 50 ml. of water and extracted with methylene chloride. After drying (sodium sulfate), the extracts were evaporated and the residue cooled to cause crystallization. Trituration with

TABLE I  
8*H*-Dibenzo[3,4:6,7]cyclohept[1,2-*d*]imidazoles (a)



No.	R	Yield %	Recryst. Solvent (b)	M.p., °C	Formula	Analyses, %				
						Calcd. H	N	C		
1	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	80	E	234-236	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O·EtOH	78.10	7.29	78.03	6.36	7.22
2	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	35	I	135-137	C <sub>24</sub> H <sub>21</sub> N <sub>3</sub> ·PrOH	78.80	10.21	79.00	6.90	10.32
3	4-ClC <sub>6</sub> H <sub>4</sub>	83	E	252-254	C <sub>22</sub> H <sub>15</sub> ClN <sub>2</sub> ·EtOH	74.12	7.21	74.05	5.34	6.90
4	CF <sub>3</sub>	0.3 (c)	-	238-240	C <sub>17</sub> H <sub>11</sub> F <sub>3</sub> N <sub>2</sub>				(d)	
5	4-COOHC <sub>6</sub> H <sub>4</sub>	48	I	271 (e)	C <sub>23</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> ·PrOH	75.70	6.79	75.67	5.71	6.49
6	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	48	E	168-170	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O	81.63	8.28	81.47	5.45	7.98
7	4-BrC <sub>6</sub> H <sub>4</sub>	67	E	252-253	C <sub>22</sub> H <sub>15</sub> BrN <sub>2</sub> ·EtOH	66.51	6.47	66.81	5.01	6.49
8	4-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	50	I	323 dec.	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> S·HCl (f)	70.66	7.17	70.43	4.97	7.03
9	C <sub>6</sub> H <sub>5</sub>	43	E	292-294	C <sub>22</sub> H <sub>16</sub> N <sub>2</sub>	85.69	9.09	85.38	5.17	8.98
10	3-Pyridyl	62	C	287-290	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub>	81.53	13.58	81.64	4.99	13.28

(a) All of these compounds were prepared by the method illustrated in the Experimental Section for compound 1. (b) E = ethanol; I = 2-propanol; C = chloroform; B = benzene; H = hexane; W = water; Bu = butanol. (c) The major product from this reaction was the corresponding oxazole. (d) Insufficient sample remained for combustion analysis. Mass spectral data indicated *m/e* 300 (calcd. 300). (e) Resolidified and remelted at 300°. (f) A hydrogen chloride salt was prepared by passing dry hydrogen chloride into a cold 2-propanol solution of product.

TABLE II  
8,9-Dihydrodibenzo[3,4:7,8]cycloocta[1,2-*d*]imidazoles (a)

No.	R	Yield %	Recryst. Solvent (b)	M.p., °C	Formula	Analyses, %					
						Calcd. C	Calcd. H	Found			
11	C <sub>6</sub> H <sub>5</sub>	22	B-H	334-335	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub>	85.68	5.63	8.69	85.62	5.74	8.38
12	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	17	B	318-320	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O	81.79	5.72	7.95	81.76	5.89	7.93
13	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	40	E	308-311	C <sub>25</sub> H <sub>23</sub> N <sub>3</sub>	82.16	6.34	11.50	81.98	6.45	11.36
14	4-ClC <sub>6</sub> H <sub>4</sub>	56	E	347-348	C <sub>23</sub> H <sub>17</sub> ClN <sub>2</sub>	77.41	4.80	7.85	77.16	5.04	7.55
15	4-COOHC <sub>6</sub> H <sub>4</sub>	48	E	340-342	C <sub>24</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> ·EtOH	75.70	5.87	6.79	75.57	5.62	6.85
16	4-BrC <sub>6</sub> H <sub>4</sub>	78	B	358-360	C <sub>23</sub> H <sub>17</sub> BrN <sub>2</sub>	68.83	4.27	6.98	68.57	4.15	6.65
17	4-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	31	E	326-329	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> S	78.22	5.47	7.60	78.00	5.71	7.29
18	3-Pyridyl	75	B	285-286	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub>	81.71	5.30	13.00	81.76	5.42	12.69
19	CF <sub>3</sub>	32 (c)	E-W	290-292	C <sub>18</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub>	68.78	4.17	8.92	68.50	4.28	8.80

(a) These compounds were prepared by the method illustrated for compound **14** in the Experimental Section. (b) See footnote b of Table I. (c) Three equivalents of trifluoroacetaldehyde ethyl hemiacetal were employed over a 6 hour reflux period.

TABLE III

Dibenzo[2,3:6,7]thiepin[4,5-*d*]imidazoles (a)

No.	R	Yield %	Recryst. Solvent (b)	M.p., °C	Formula	Analyses, %					
						Calcd. C	Calcd. H	Found			
20	C <sub>6</sub> H <sub>5</sub>	16	I-W	312 dec.	C <sub>21</sub> H <sub>14</sub> N <sub>2</sub> S·HCl	69.50	4.17	7.72	69.81	4.29	7.82
21	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	73	I-W	300 dec.	C <sub>22</sub> H <sub>16</sub> N <sub>2</sub> OS·HCl	67.25	4.36	7.13	67.18	4.40	6.94
22	4-BrC <sub>6</sub> H <sub>4</sub>	56	I-W	334 dec.	C <sub>21</sub> H <sub>13</sub> BrN <sub>2</sub> S·HCl	57.09	3.19	6.34	56.91	3.50	5.98
23	4-ClC <sub>6</sub> H <sub>4</sub>	46	I-W	323 dec.	C <sub>21</sub> H <sub>13</sub> ClN <sub>2</sub> S·HCl	63.48	3.55	7.05	63.18	3.80	6.89
24	4-COOHC <sub>6</sub> H <sub>4</sub>	59	Bu-W	300 dec.	C <sub>22</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S·HCl	64.94	3.72	6.89	64.89	4.00	6.80
25	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	42	I-W	321 dec.	C <sub>23</sub> H <sub>19</sub> N <sub>3</sub> S·HCl·0.5H <sub>2</sub> O	66.57	5.10	10.13	66.87	5.18	9.90
26	CF <sub>3</sub>	51 (c)	B	257 dec.	C <sub>16</sub> H <sub>9</sub> F <sub>3</sub> N <sub>2</sub> S	60.37	2.85	8.80	60.38	3.13	8.55
27	3-Pyridyl	54	I-W	230 dec.	C <sub>20</sub> H <sub>13</sub> N <sub>3</sub> S·HCl	66.01	3.88	11.55	65.88	4.12	11.25

(a) These compounds were prepared by the method illustrated for compound **22** in the Experimental Section. (b) See footnote b of Table I. (c) Three equivalents of trifluoroacetaldehyde ethyl hemiacetal were employed over a 3 hour reflux period.

hexane yielded, in two crops, 0.17 g. (37%) of VIII, m.p. 69-72° (lit. (5) m.p. 72-73°); mass spectrum  $m/e$  226 (calcd. 226), 225, 197 (loss of  $C\equiv O$ ), 193, 165.

Several attempts to carry out this cyclodehydration in polyphosphoric acid (5) gave only low yields of impure product.

10,11-Dihydrodibenzo[*b,f*]thiepin-10,11-dione (IX).

To a suspension of 2.6 g. (0.0325 mole) of selenium dioxide in 25 ml. of acetic acid was added a solution of 6.7 g. (0.0296 mole) of VIII (5) in 100 ml. of acetic acid. The suspension was heated (steam heat) for 1½ hours and then filtered. The red filtrate was diluted with 100 ml. of water, neutralized with solid sodium bicarbonate and extracted repeatedly with ethyl acetate. The extracts were dried (sodium sulfate) and evaporated to a yellow solid. After trituration with diethyl ether, there was obtained 3.2 g. (45%) of yellow IX, m.p. 124-126°; mass spectrum: 240 (calcd. 240), 212 (loss of  $C\equiv O$ ), 184 (loss of 2  $C\equiv O$ ).

*Anal.* Calcd. for  $C_{14}H_8O_2S$ : C, 69.99; H, 3.35. Found: C, 70.03; H, 3.48.

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