The Synthesis of Heterocyclic Derivatives of Dibenzo[*a,d*]cycloheptene

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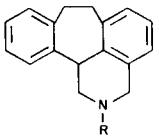
Received February 5, 1979

The synthesis of 2-amino-7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-*de*]quinazoline (**10**) and 6,7-dihydrobenzo[1,2]cyclohepta[3,4,5-*cd*]indazole (**5**) is described.

J. Heterocyclic Chem., **16**, 681 (1979).

Several heterocyclic derivatives of dibenzo[*a,d*]cycloheptene have been reported (1-5); some of these having pharmacological activity (**1** and **2**) (1,2).



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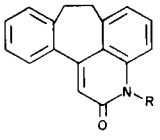

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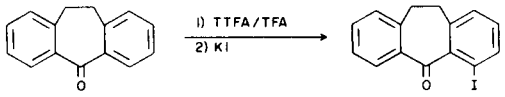
Our interest in phenothiazines (6-8) and their isosteric analogues coupled with our recent observation (9) of the thallation-iodination of dibenzosuberone (**3**) to the 4-iodo derivative **4** (Scheme I) prompted us to study **4** as a possible convenient starting material for the synthesis of other such heterocycles.

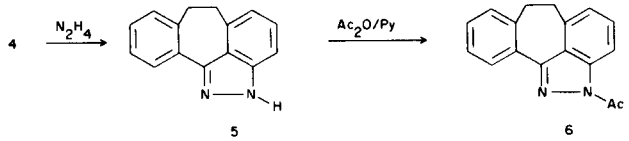
Scheme I



3 4

As **4** contains both a carbonyl group for imine formation plus a proximate substitution-activated iodine atom, we felt that treatment with suitable terminal-diamino reagents should lead to heterocyclic systems in one-pot reactions. The simplest and obvious first reagent to be tested was hydrazine, which reacted with **4** giving a 26% yield of the corresponding indazole **5**, which was subsequently transformed into the *N*-acetyl derivative **6** (Scheme II).

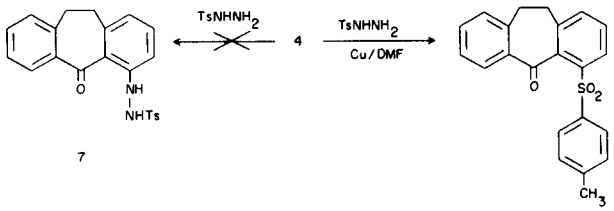
Scheme II



5 6

In an attempt to prepare **5** *via* a multistep reaction sequence, we treated **4** with tosylhydrazide, but only recovered starting material. Repeating the treatment in DMF at reflux in the presence of copper powder led to reaction, but instead of the expected derivative **7**, we obtained the diaryl sulfone **8** (Scheme III).

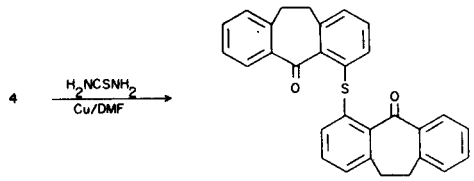
Scheme III



7 8

All attempts to affect reaction of **4** with hydroxylamine or urea were unsuccessful. Treatment of **4** with thiourea under Ullmann conditions did lead to reaction, however, the only product isolated (34% yield) was assigned the structure of the thioether **9** (Scheme IV).

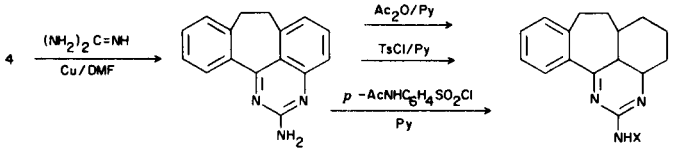
Scheme IV



9

Unwilling to abandon the problem, we finally tried guanidine, which reacted with **4** giving a 53% yield of the desired aminoquinazoline derivative **10**. The transformation of **10** into various *N*-substituted derivatives (**11a-c**) was readily accomplished in high yields (Scheme V).

Scheme V



10

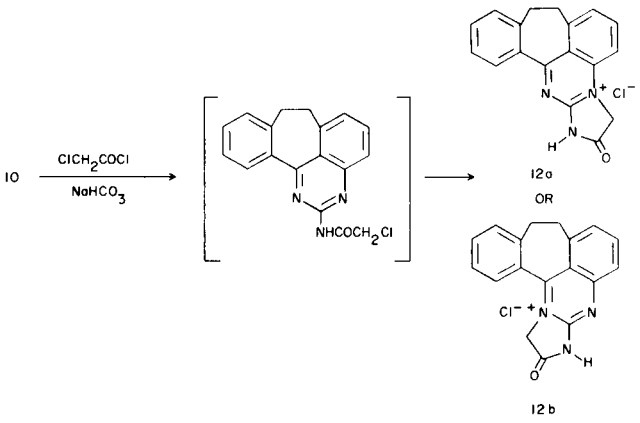
11a, X = Ac-
b, X = Ts-
c, X = *p*-AcNHC$_6$H$_4$SO$_2$-

The reaction of **10** with chloroacetyl chloride resulted in *N*-acylation followed by alkylation-cyclization to the quinazolinium salt **12**. That cyclization indeed occurred is

0022-152X/79/040681-03$02.25

supported by several observations. The solubility of **12** in organic solvents is much lower than that of the *N*-acetyl derivative **11a**. The carbonyl stretch in the ir spectrum of **11a** is at 1670 cm^{-1}, whereas for **12** the absorption occurs at 1705 cm^{-1}, consistent with a γ-lactam structure. Although two possible sites exist for cyclization, a study using molecular models indicates reaction at N-3 should be sterically less hindered, thus our tentative assignment is structure **12a** (Scheme VI).

Scheme VI



EXPERIMENTAL

The ir spectra were obtained on a Perkin-Elmer model PE 137 spectrophotometer. The pmr spectra were recorded on a Hitachi Perkin-Elmer R-20B (60 MHz) nuclear magnetic resonance spectrometer. All melting points are uncorrected.

6,7-Dihydrobenzo[1,2]cyclohepta[3,4,5-*cd*]indazole (**5**).

A mixture of 1.0 g. of **4** (9) in 15 ml. of 85% hydrazine hydrate was heated at reflux for 24 hours then cooled and poured into 100 ml. of water. The mixture was extracted with chloroform (3 x 100 ml.), and the combined extracts dried over magnesium sulfate then evaporated at reduced pressure. The resulting oil was chromatographed over silica gel with benzene giving 170 mg. (26%) of colorless crystals, m.p. 162-163°; ir (potassium bromide): 3260 cm^{-1} (NH); pmr (deuteriochloroform): δ 8.15-8.32 (m, 1, ArH), 6.76-7.38 (m, 7, ArH + NH) and 3.18 (s, 4, CH_2CH_2).

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.90; H, 5.50; N, 12.81.

Reaction of **5** with Acetic Anhydride (**6**).

A mixture of 80 mg. of **5** and 0.5 ml. of acetic anhydride in 15 ml. of pyridine was stirred for 6 hours and then evaporated at reduced pressure. The resulting solid was recrystallized from *n*-hexane-benzene giving 90 mg. (97%) of colorless crystals, m.p. 105-106°; ir (potassium bromide): 1720 cm^{-1} (C=O); pmr (deuteriochloroform): δ 8.21-8.40 (m, 1, ArH), 7.01-7.59 (m, 6, ArH), 3.20 (s, 4, CH_2CH_2) and 2.85 (s, 3, CH_3).

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.94; H, 5.52; N, 10.55. Found: C, 77.84; H, 5.38; N, 10.68.

Reaction of **4** with Tosylhydrazide (**8**).

A stirred mixture of 1.0 g. of **4**, 570 mg. of tosylhydrazide and 70 mg. of copper powder in 25 ml. of dimethylformamide was heated at reflux for 10 hours then poured into 100 ml. of water. The mixture was extracted with 200 ml. of ether and the extract washed with water (3 x 100 ml.), dried over magnesium sulfate and then evaporated at reduced pressure. The resulting solid was recrystallized from *n*-hexane-benzene giving 590 mg. (53%) of colorless crystals, m.p. 180°; ir (potassium bromide): 1670 cm^{-1} (C=O) and 1290 cm^{-1} (SO_2); pmr (acetic acid-d_4/trifluoroacetic acid): δ 7.01-8.20 (m, 14, ArH), 3.12 (s, 4, CH_2CH_2) and 2.40 (s, 3, CH_3).

Anal. Calcd. for $C_{23}H_{18}O_3S$: C, 72.90; H, 5.01. Found: C, 72.85; H, 5.02.

Reaction of **4** with Thiourea (**9**).

A mixture of 1.0 g. of **4**, 200 mg. of thiourea and 100 mg. of copper powder in 25 ml. of dimethylformamide was heated at reflux for 12 hours then cooled and poured into 100 ml. of water. The mixture was extracted with 100 ml. of ether and the extract washed with water (4 x 100 ml.) then dried over magnesium sulfate and evaporated at reduced pressure. The resulting oil was chromatographed over silica gel with benzene giving a yellow solid which was recrystallized from *n*-hexane-benzene furnishing 450 mg. (34%) of colorless crystals, m.p. 178-179°; ir (potassium bromide): 1660 cm^{-1} (C=O); pmr (deuteriochloroform): δ 6.82-7.42 (m, 14, ArH) and 2.95 (s, 8, CH_2CH_2).

Anal. Calcd. for $C_{30}H_{22}O_2S$: C, 80.69; H, 4.97. Found: C, 80.50; H, 5.00.

2-Amino-7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-*de*]quinazoline (**10**).

A stirred mixture of 1.0 g. of **4**, 190 mg. of guanidine nitrate, 100 mg. of copper powder and 50 mg. of potassium hydroxide in 25 ml. of dimethylformamide was heated at reflux for 12 hours. After cooling, the mixture was poured into 100 ml. of water and extracted with 100 ml. of ether. The etheral extract was washed with water (4 x 100 ml.), dried over magnesium sulfate and evaporated at reduced pressure. The resulting yellow solid was recrystallized from *n*-hexane-benzene furnishing 390 mg. (53%) of yellow crystals, m.p. 174-175°; ir (potassium bromide): 3480 cm^{-1} (NH) and 1670 cm^{-1} (C=N); pmr (deuteriochloroform): δ 7.98-8.13 (m, 1, ArH), 6.85-7.43 (m, 6, ArH), 5.44 (s, 2, $-NH_2$) and 2.93-3.45 (m, 4, CH_2CH_2).

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.49; N, 12.72. Found: C, 77.54; H, 5.50; N, 12.82.

Reaction of **10** with Acetic Anhydride (**11a**).

A mixture of 100 mg. of **10** and 0.7 ml. of acetic anhydride in 15 ml. of pyridine was stirred for 6 hours then evaporated at reduced pressure. The resulting yellow solid was recrystallized from *n*-hexane-benzene giving 92 mg. (88%) of light yellow crystals, m.p. 202-203°; ir (film): 3325 cm^{-1} (NH) and 1670 cm^{-1} (C=O); pmr (deuteriochloroform): δ 8.05-8.19 (m, 1, ArH), 7.09-7.63 (m, 7, ArH + NH), 2.97-3.45 (m, 4, CH_2CH_2) and 2.58 (s, 3, CH_3).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.72; H, 5.26; N, 14.40.

Reaction of **10** with Tosyl Chloride (**11b**).

A mixture of 100 mg. of **10** and 80 mg. of tosyl chloride in 25 ml. of pyridine was stirred for 10 hours. After evaporation of solvent at reduced pressure, the product was recrystallized from *n*-hexane-2-propanol giving 125 mg. (77%) of light yellow crystals, m.p. 227-230° dec.; ir (potassium bromide): 3350 cm^{-1} (NH) and 1240 cm^{-1} (SO_2); pmr (trifluoroacetic acid): δ 7.18-8.20 (m, 12, ArH + NH), 3.11-3.67 (m, 4, CH_2CH_2) and 2.40 (s, 3, CH_3).

Anal. Calcd. for $C_{25}H_{19}N_3O_2S$: C, 68.71; H, 4.77; N, 10.47. Found: C, 68.78; H, 5.00; N, 10.18.

Reaction of **10** with *p*-Acetamidobenzenesulfonyl Chloride (**11c**).

A mixture of 100 mg. of **10** and 95 mg. of **p**-acetamidobenzenesulfonyl chloride in 15 ml. of pyridine was stirred for 10 hours and then evaporated at reduced pressure. The product was recrystallized from *n*-hexane-2-propanol giving 140 mg. (78%) of yellow crystals, m.p. 280-283°; ir (potassium bromide): 3300 cm^{-1} (NH) and 1240 cm^{-1} (SO_2); pmr (trifluoroacetic acid): δ 9.11 (s, 1, NH), 7.29-8.15 (m, 12, ArH + NH), 3.12-3.65 (m, 4, CH_2CH_2) and 2.44 (s, 3, CH_3).

Anal. Calcd. for $C_{24}H_{19}N_4O_3S$: C, 64.85; H, 4.54; N, 2.61. Found: C, 64.81; H, 4.83; N, 2.54.

Reaction of **10** with Chloroacetyl Chloride (**12**).

A mixture of 100 mg. of **10**, 0.8 ml. of chloroacetyl chloride and 50 mg. of sodium bicarbonate in 15 ml. of benzene was stirred for 2 hours. The mixture was washed in 30 ml. of water, dried over magnesium sulfate and

evaporated at reduced pressure. The product was recrystallized from benzene giving 110 mg. (85%) of yellow crystals, m.p. 205-207° dec.; ir (potassium bromide): 2360 cm^{-1} (NH) and 1705 cm^{-1} (C=O); pmr (deuteriochloroform): δ 8.21-8.39 (m, 1, ArH), 7.21-7.83 (m, 7, ArH + NH), 4.75 (s, 2, CH_2) and 3.00-3.51 (m, 4, CH_2CH_2).

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98. Found: C, 66.57; H, 4.28; N, 12.83.

Acknowledgment.

We thank the Secretary of Planning (FINEP) and the National Council of Scientific and Technological Development (CNPq) for their support of this work.

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