Preparation of 1,7-Disubstituted Indan Derivatives and Their Application to the Synthesis of Tricyclic Heterocyclic Compounds

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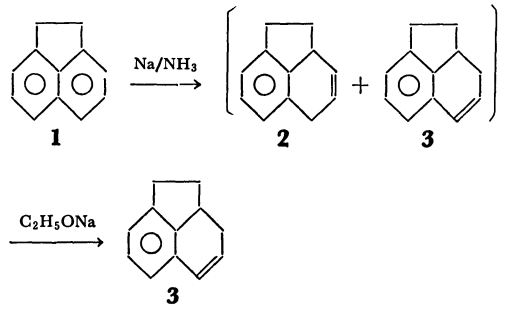
The Birch reduction of acenaphthene (**1**) followed by treatment of the reduction product with sodium ethoxide gave 2a,3-dihydroacenaphthene (**3**). The oxidation of **3** with hydrogen peroxide gave 2a,3,4,5-tetrahydroacenaphthene-4,5-diol (**5**). Further oxidation of **5** afforded various 1,7-disubstituted indan derivatives including 7-carboxyindan-1-acetic acid (**7**). Two tricyclic *N*-heterocyclic compounds, 3,3a-dihydrocyclopent[*de*]quinolin-2(1*H*)-one (**13**) and 3,3a-dihydrocyclopent[*de*]isoquinolin-1(2*H*)-one (**17**), were synthesized from **7**.

1,7-Disubstituted indan derivatives might be useful synthetic intermediates, since they can be converted into compounds of various structures. Rapoport and Pasky[1] synthesized the fused tricyclic compounds containing one six- and two five-membered rings, utilizing 1,7-disubstituted indan derivatives as key intermediates. However, their method of preparation involved a lengthy route starting from indene.

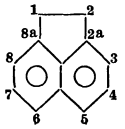
In this paper, we describe an alternative method for the preparation of 1,7-disubstituted indan derivatives and their application to the synthesis of tricyclic *N*-heterocycles, very rare type of compounds. Our method involves the Birch reduction of acenaphthene and an oxidative cleavage of the reduction product as key steps.

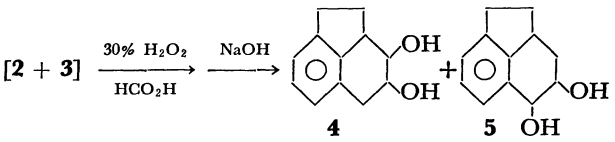
Results and Discussion

Preparation of 1,7-Disubstituted Indan Derivatives. The reduction of acenaphthene (**1**)* with calcium hexammine in ether and with a large excess of sodium in liquid ammonia gave 2a,3,4,5-tetrahydroacenaphthene.[2,3] However, we found that the Birch reduction of **1** by use of 2.3—2.4 molar equivalents of sodium in liquid ammonia afforded a mixture of 2a,5-dihydro- and 2a,3-dihydroacenaphthene (**2** and **3**) in a 90% yield. Treatment of the mixture with sodium ethoxide in ethanol gave **3** practically in a pure state. That the product obtained by the Birch reduction of **1** consists of a mixture of **2** and **3** is suggested from the fact that treatment of the reduction product with

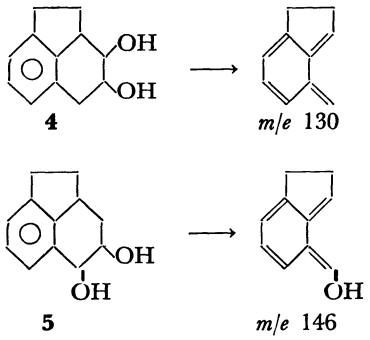


* The numbering system used for acenaphthene (**1**) is shown in the formula.

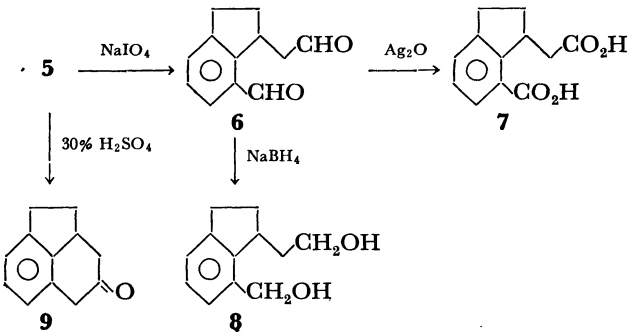




hydrogen peroxide in formic acid followed by hydrolysis gave a mixture of 2a,3,4,5-tetrahydroacenaphthene-3,4-diol (**4**) and 2a,3,4,5-tetrahydroacenaphthene-4,5-diol (**5**) which were separated by repeated recrystallization. The hydrogen peroxide oxidation of a pure sample of **3** afforded **5** in a 70% yield. The structures of **4** and **5** were confirmed by the fragmentation patterns in their mass spectra, which show the base peaks at *m/e* 130 and 146, respectively. These ions could be formed by the retro-Diels-Alder cleavage of the compounds, corresponding respectively to the loss of $C_2H_4O_2$ and C_2H_4O fragments.

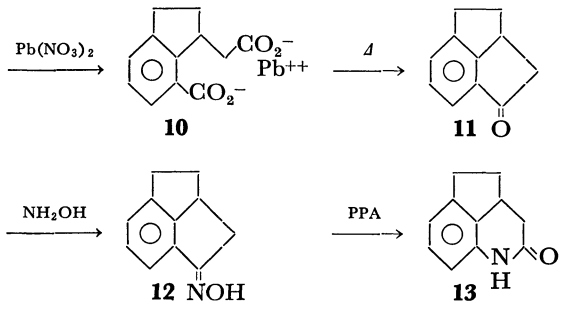


The oxidation of **5** with sodium metaperiodate in an aqueous ethanol gave 7-formylindan-1-acetaldehyde (**6**) in an 86% yield. The IR spectrum (film) of **6** showed carbonyl absorptions at 1690 and 1720 cm^{-1}. Its NMR spectrum (CCl_4) showed a multiplet at δ 9.9 due to an aliphatic aldehyde proton and a singlet at δ 10.2 due to an aromatic aldehyde proton. Treatment



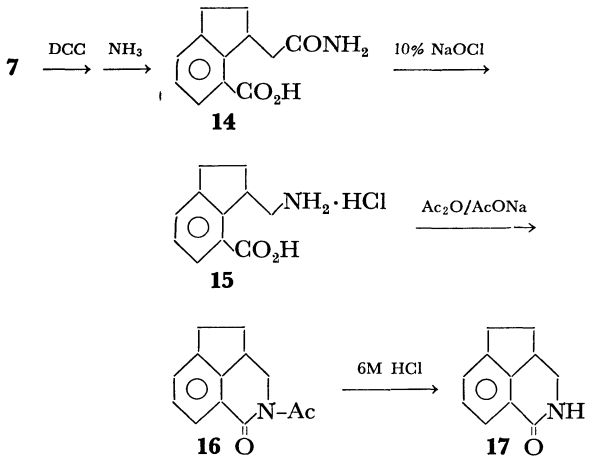
of **6** with silver oxide gave 7-carboxyindan-1-acetic acid (**7**) in an 88% yield. The dicarboxylic acid **7** has been synthesized starting from indene.[1] The reduction of **6** with sodium borohydride gave 1-(2-hydroxyethyl)-7-hydroxymethylindan (**8**) in a 78% yield. When **5** was refluxed in 30% sulfuric acid, 2a, 3,4,5-tetrahydroacenaphthen-4-one (**9**) was obtained in a 58% yield. IR spectrum (KBr) of **9** showed a carbonyl absorption at 1710 cm^{-1} and its NMR spectrum a singlet at δ 3.38 attributable to two methylene protons at C-5.

Synthesis of Heterocyclic Compounds. By the method of Rapoport and Pasky,[1] **7** was converted into 2,2a-dihydro-1-oxo-1H-cyclopent[*cd*]indene (**11**) *via* the lead salt (**10**). The transformation of **11** to its oxime **12**, followed by treatment with polyphosphoric acid



(PPA) afforded 3,3a-dihydrocyclopent[*de*]quinolin-2(1*H*)-one (**13**) in a 28% yield. The IR spectrum (KBr) of **13** showed absorptions at 3200, 1690 and 1630 cm^{-1} due to the amide group. The heterocyclic compound **13** was synthesized by Fuson and Veazey[4] from β-(*o*-nitrophenyl)glutaric acid. The melting point of **13** we obtained was in good agreement with theirs.[4]

We attempted to synthesize 3,3a-dihydrocyclopent-[*de*]isoquinolin-1(2*H*)-one (**17**), a structural isomer of **13**.



Treatment of **7** with *N,N'*-dicyclohexylcarbodiimide (DCC) followed by the addition of concentrated aqueous ammonia gave 7-carboxyindan-1-acetamide (**14**) in a 70% yield. The Hofmann rearrangement of **14** was carried out by use of sodium hypochlorite in an aqueous sodium hydroxide. Acidification of the rearranged product gave 7-carboxyindan-1-methylamine hydrochloride (**15**) which could not be purified. Treatment of the crude **15** with acetic anhydride containing sodium acetate afforded 2-acetyl-3,3a-dihydrocyclopent[*de*]isoquinolin-1(2*H*)-one (**16**) in a good yield. The IR spectrum (KBr) of **16** showed an amidecarbonyl absorption at 1690 cm^{-1} and no absorptions due to NH group, its NMR spectrum (CCl_4) a sharp singlet at δ 2.47 due to three methyl protons of the acetyl group, and its mass spectrum the parent peak at *m/e* 215. Hydrolysis of **16** with 6M hydrochloric acid gave a mixture of **17** (37%) and **15** (32%). The IR spectrum (KBr) of **17** showed absorptions characteristic of the amide group at 3200, 1670 and 1590 cm^{-1}, and its mass spectrum the parent peak at *m/e* 173.

Experimental

*Birch Reduction of Acenaphthene (**1**).* A solution of 40 g (0.26 mol) of **1** in 150 ml of dry ether was added rapidly to a stirred solution of 14 g (0.61 mol) of sodium in 400 ml of liquid ammonia at −70 °C, and the mixture was stirred for 3 hr at the same temperature. Excess ammonium chloride was added to this mixture, and ammonia was then evaporated at room temperature. Water and then ether were added to the residue. The ether layer was separated, washed with water, dried over Na_2SO_4, and then evaporated. The residual oil was distilled to yield 37 g of a pale yellow oil consisting of a mixture of **3** and **4**, bp 58—59 °C/0.15 mmHg. IR(film): 3020, 2940, 2840, 1600, 1460, 1435, 800, 760, 715, and 690 cm^{-1}. NMR(CCl_4): δ 1.3—2.0(1H, m), 2.1—2.7(2H, m), 2.7—3.1(2H, m), 3.0—3.5(2H, m), 5.7—6.1(1.6H, m), 6.5 (0.4H, dd, J=10.0 and 3.0 Hz), and 6.65—7.15 ppm(3H, m).

*2a,3-Dihydroacenaphthene (**3**).* A solution of sodium ethoxide was prepared by adding 34.5 g (1.5 g-atom) of sodium to 500 ml of absolute ethanol. To this was added 46.8 g of the Birch reduction product, and the mixture was refluxed for 3 hr under nitrogen atmosphere. Most of the ethanol was removed, and then ice-water was added to the residue. The resulting mixture was extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated. Distillation of the residue gave 42.1 g of **3** as a colorless oil, bp 73—74 °C/0.5 mmHg. The yield of **3** from **1** was 81%. IR(film): 3030, 2940, 2840, 1630, 1600, 1480, 1460, 1435, 800, 790, 750, and 690 cm^{-1}. NMR(CCl_4): δ 1.3—2.0 (2H, m, CH_2 at C-3), 2.1—2.7 (2H, m, CH_2 at C-2), 2.7—3.0(2H, m, CH_2 at C-1), 3.0—3.5(1H, m, CH at C-2a), 5.9(1H, bd, J=10.0 Hz, vinyl proton at C-4), 6.5(1H, dd, J=10.0 and 3.0 Hz, vinyl proton at C-5), and 6.65—7.15 ppm(3H, m, aromatic H).

*2a,3,4,5-Tetrahedroacenaphthene-4,5-diol (**5**).* To a stirred mixture of 30 g (0.19 mol) of **3** in 12 ml of 95% HCO_2H was added 26.5 g of 30% H_2O_2 at 20—25 °C. The reaction mixture was stirred for 1 hr at the same temperature, poured into 500ml of water, then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 10% $NaHCO_3$ solution, dried over Na_2SO_4, then evaporated to give a white solid. Since its IR spectrum(KBr) showed a carbonyl absorption due to the ester group at 1700 cm^{-1}, the solid was subjected to hydrolysis. To a stirred solution of the solid in 100ml of ethanol was added 65 ml of 20% NaOH solution under ice-cooling. The mixture was stirred for 5 hr at room temperature and diluted with 500 ml of water. The resulting brown solid was filtered, washed thoroughly with water to give 26 g (71%) of **5**. Recrystallization from benzene-ethanol gave pure **5** as white crystals, mp 138—139 °C. IR(KBr): 3320 cm^{-1}(OH). NMR($(CD_3)_2CO$): δ 1.3—1.9(2H, m), 2.65—3.0(2H, m), 3.0—3.5(1H, m), 3.85—4.3(3H, m), 4.55(1H, dd, J=5.6 and 3.1 Hz), and 7.2 ppm(3H, bs). Mass: *m/e* 190(M^+).

Found: C, 75.54; H, 7.58%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

Hydrogen Peroxide Oxidation of the Birch Reduction Product. The Birch reduction product (30 g) was treated with H_2O_2-HCO_2H and then with NaOH solution in the same manner as described above. The resulting mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a brown viscous oil which was solidified upon treatment with CCl_4. The solid was collected by filtration to give 11.5 g of crude **4**, mp 130—137 °C. The crude **4** was recrystallized from benzene to give an analytical sample, mp 139—141 °C. IR(KBr): 3350 cm^{-1}(OH). NMR($(CD_3)_2CO$): δ 2.55—3.05(4H, m), 3.28(1H, m), 3.62(1H, m), 3.84—4.4(3H, m), and 6.75—7.15 ppm(3H, m). Mass: *m/e* 190(M^+).

Found: C, 75.62; H, 7.46%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

The CCl_4 filtrate was evaporated to give a brown viscous oil. Distillation of this oil gave yellow viscous oil of bp 140—150 °C/0.2 mmHg, which upon trituration with benzene yielded a white solid. The solid was recrystallized from $CHCl_3$ to give **5** as white crystals, mp 138—140 °C.

*7-Formylindan-1-acetaldehyde (**6**).* A soluiton of 12.8 g (0.06 mol) of sodium metaperiodate in 200 ml of water was added over 30 min to a stirred solution of 9.5 g (0.05 mol) of **5** in 200 ml of ethanol at 15—20 °C. Stirring was continued for 20 hr at room temperature, and most of the ethanol was evaporated under reduced pressure at room temperature. The resulting yellow oil was diluted with water, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The resulting oil was distilled to afford 8.1 g (86%) of **6** as a colorless oil, bp 117—119 °C/0.3 mmHg, which upon standing in a refrigerator gave a white solid. IR(film): 1720(C=O) and 1690 cm^{-1}(C=O). NMR(CCl_4): δ 1.7—2.75(4H, m), 2.75—3.3(2H, m), 4.0—4.6(1H, m, CH at C-1), 7.3—7.9(3H, m, aromatic H), 9.9 (1H, m, aliphatic CHO), and 10.2 ppm(1H, s, aromatic CHO).

Found: C, 76.49; H, 6.57%. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43%.

The semicarbazone of **6** was prepared by the usual method and recrystallized from ethanol-water, mp 200—202 °C(decomp.).

Found: C, 55.71; H, 6.18; N, 28.04%. Calcd for $C_{14}H_{18}N_6O_2$: C, 55.61; H, 6.00; N, 27.80%.

*7-Carboxyindan-1-acetic Acid (**7**).* A solution of 210 ml of 1M NaOH solution was added over 30 min to a stirred mixture of 4.3 g (0.023 mol) of **6** and 17.6 g(0.134 mol) of $AgNO_3$ in 100 ml of 50% aqueous ethanol under cooling with an ice-water bath. After stirring for 30 min, air was passed into the stirred reaction mixture for 6 hr at room temperature. A black solid was separated by decantation and washed several times with 5% NaOH solution. All the aqueous solutions were combined and washed with ether. The aqueous solution was acidified with 6 M HCl to give a white solid which was separated, washed with water, and dried *in vacuo* to yield 4.6 g (88%) of **7**, mp 178—181 °C. An analytical sample of **7** was obtained by recrystallization from water-ethanol, mp 181—184 °C (lit,[1] mp 190—191 °C). IR(KBr): 3600—2500(OH), 1690(C=O), and 1670 cm^{-1} (C=O).

Found: C, 66.01; H, 5.31%. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%.

*1-(2-Hydroxyethyl)-7-hydroxymethylindan (**8**).* To a solution of 500 mg(2.66 mmol) of **6** in 10 ml of ethanol was added 76 mg(2.0 mmol) of $NaBH_4$, and the reaction mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, and the colorless viscous residue was added to ice-water and then extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a colorless viscous oil, which upon scratching with a spatula solidified to yield 400 mg (79%) of crude **8**. The crude solid was recrystallized from CCl_4 to yield white crystals, mp 54—56 °C. IR(KBr): 3200 cm^{-1} (OH). NMR($CDCl_3$): δ 1.3—2.3(4H, m), 2.6—3.0(2H, m), 3.0—3.4(1H, m), 3.55(2H, t, J=6.2 Hz, $-CH_2\mathbf{CH_2}OH$), 3.95(2H, bs, two of OH), 4.55(2H, s, Ar-$\mathbf{CH_2}OH$), and 7.05 ppm(3H, bs, aromatic H).

Found: C, 74.75; H, 8.36%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

*2a,3,4,5-Tetrahydroacenaphthen-4-one (**9**).* A mixture of 1.9 g (0.01 mol) of **5** and 200 ml of 30% aqueous H_2SO_4 was refluxed for 2 hr, cooled to room temperature, and then diluted with 150 ml of ice-water. The aqueous solution was extracted with ether, and the extract was washed with water, dried over Na_2SO_4, and evaporated. The resulting brown solid was sublimed at 100 °C under 0.5 mmHg to give 1.0 g (58%) of **9** as a white solid, mp 48—51 °C. IR(KBr): 1710 cm^{-1} (C=O). NMR(CCl_4): δ 1.2—3.3(7H, m), 3.38(2H, s, CH_2 at C-5), and 6.75—7.3 ppm(3H, m, aromatic H).

The oxime of **9** was prepared in the usual manner and purified by recrystallization from cyclohexane, mp 129—131 °C.

Found: C, 77.10; H, 6.95; N, 7.51%. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48%.

2,2a-Dihydro-1-oxo-1H-cyclopent[cd]*indene (**11**).* This was prepared from **7** *via* its lead salt (**10**) by the method of Rapoport and Pasky,[1] mp 59—61 °C (lit.[1] mp 63 °C).

2,2a-Dihydro-1-hydroxyimino-1H-cyclopent[cd]*indene (**12**).* This was prepared from 1.5 g (22 mmol) of hydroxylamine hydrochloride and 590 mg (3.7 mmol) of **11** by the usual method. The yield of **12** was quantitative. A pure sample was obtained by recrystallization from water-ethanol, mp 130—132 °C. IR(KBr): 1660 cm^{-1} (C=N).

Found: C, 76.04; H, 6.43; N, 8.08%. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09%.

3,3a-Dihydrocyclopent[de]*quinolin-2(1H)-one (**13**).* Polyphosphoric acid (PPA) was prepared by stirring a mixture of 12 g of 85% H_3PO_4 and 16 g of P_2O_5 at 130—140 °C for 2 hr, and then 1.8 g (14 mmol) of **12** was added at 80—100 °C. The reaction mixture was stirred at the same temperature for 15 min and then chilled. Ice-water was added to the reaction mixture until PPA was dissolved. The resulting solid was collected by filtration and recrystallized from *n*-hexane-$CHCl_3$ to give 500 mg (28%) of **13**, mp 163—164 °C (lit,[4] mp 163—164 °C). IR(KBr): 3200, 1690, 1630, 1605, 1490, 1330, and 770 cm^{-1}. NMR($CDCl_3$): δ 1.4—3.1(6H, m), 3.1—3.6(1H, 6.5—7.1(3H, m, aromatic H), and 9.1—9.5 ppm(1H, bs, NH).

Found: C, 76.33; H, 6.47; N, 8.04%. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09%.

*7-Carboxyindan-1-acetamide (**14**).* To a solution of 1.05 g (5.4 mmol) of *N,N'*-dicyclohexylcarbodiimide in 15 ml of dry dioxane was added 1.0 g (4.5 mmol) of **7**. The reaction mixture was allowed to stand at room temperature for 1.5 hr. The resulting *N,N'*-dicyclohexylurea was removed by filtration and the filtrate was evaporated under reduced pressure to give a pale yellow viscous oil; its IR spectrum showed absorptions characteristic of an acid anhydride at 1790 and 1720 cm^{-1}. A concentrated aqueous ammonia (30 ml) was added to the acid anhydride under ice-cooling. The mixture was allowed to stand at room temperature for 3 hr, warmed on a water bath for 30 min, and then extracted with CH_2Cl_2. The aqueous solution was acidified with concentrated HCl. The resulting solid was collected by filtra-

tion, washed with water and dried to give 700 mg(70%) of crude **14**, mp 194—200 °C. An analytical sample was obtained recrystallization from ethanol, mp 209—212 °C. IR(KBr): 3400, 3200, 1690, and 1650 cm^{-1}.

Found: C, 65.85; H, 6.08; N, 6.44%. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

*7-Carboxyindan-1-methylamine Hydrochloride (**15**).* To a solution of 2.2 g (0.01 mol) of **14** in 30 ml of 10% aqueous NaOH solution was added 9.7 g of 10% aqueous sodium hypochlorite solution at room temperature. The reaction mixture was stirred at room temperature for 15 min, at 55 °C for 1 hr, and at 70—80 °C for 30 min. It was then washed with CH_2Cl_2. The aqueous solution was acidified to pH 1.0 with concentrated HCl. The acidified solution was again washed with CH_2Cl_2, and the resulting brown solid was collected by filtration. When the filtrate was concentrated to one-half its initial volume, a second crop of the solid was obtained. All the solids were combined and used without further purification for the preparation of **16**. The solids thus obtained weighed 2.1 g and decomposed at 230—240 °C. IR(KBr): 3100—2500, 1680, and 1630 cm^{-1}.

2-Acetyl-3,3a-dihydrocyclopent[de]*isoquinolin-1(2H)-one (**16**).* A mixture of 1.5 g of crude **15**, 900 mg of anhydrous AcONa, and 5 ml of Ac_2O was refluxed for 20 min. A large excess of 10% NaOH solution was added to the cooled mixture. The resulting mixture was heated for 15 min, and then extracted with ether. The ether extract was washed with $NaHCO_3$ solution, dried over Na_2SO_4, then evaporated to give 1.0 g (70%) of a pale yellow solid. Recrystallization of the solid from methanol–water gave an analytical sample of **15**, mp 74—76 °C. IR(KBr): 1690, 1600, 1370, 1300, 1235, 1225, and 755 cm^{-1}. NMR(CCl_4): δ 1.4—2.0(1H, m), 2.2—2.8(1H, m), 2.47(3H, s), 2.8—3.6(4H, m), 4.9(1H, dd, J= 10.0 and 4.0 Hz), and 7.1—7.8 ppm(3H, m). Mass: *m/e* 215(M^+).

Found: C, 72.49; H, 6.16; N, 6.46%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%.

3,3a-Dihydrocyclopent[de]*isoquinolin-1(2H)-one (**17**).* A mixture of 1.0 g (4.6 mmol) of **16** and 50 ml of 6 M HCl was refluxed for 2 hr, and then extracted with $CHCl_3$. During this operation a white solid appeared and was collected by filtration to yield 350 mg (32%) of **15**.

The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and then evaporated to give 300 mg (37%) of a brown solid. The solid was recrystallized from *n*-hexane–$CHCl_3$ to give **17** as white crystals, mp 150—152 °C. IR (KBr): 3200, 1670, 1610, 1595, 1490, 1400, 1350, 1320, 800, and 760 cm^{-1}. Mass: *m/e* 173(M^+).

Found: C, 76.37; H, 6.60; N, 8.05%. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09%.

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