21308-88-3; **8**, 21308-89-4; **10**, 21308-90-7; **11**, 21308-91-8; **13**, 21308-92-9; **14**, 21308-93-0; **17**, 21308-94-1; **18**, 21308-95-2; **20**, 21308-96-3; **21**, 21308-97-4; **22**, 21308-98-5; **25**, 21308-99-6; **26**, 21309-00-2; **27**, 21309-01-3.

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Alternate Precursors in Biogenetic-type Syntheses. V.[1] 3-(Indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline as a Precursor. The Synthesis and Stereochemistry of 2-Methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-one

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A biogenetic-type synthesis employing 3-(indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**) as an alternate precursor in place of the corresponding 1-(indol-3-ylmethyl) analog is described. Birch reduction of **2** followed by acid-catalyzed hydrolysis and cyclization leads to the formation of a mixture of epimeric 2-methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-ones (**7a** and **7b**), which differ only in the configuration at C-4. Chemical and spectroscopic evidence indicates the higher melting ketone (major product) to have the geometry of a *trans*-decahydroisoquinoline (**7a**), the other being a *cis*-decahydroisoquinoline (**7b**).

Earlier publications in this series have described the use of 1-(indol-3-ylmethyl)isoquinoline derivatives as alternative precursors[2] for the biogenetic-type synthesis[3] of missing alkaloid systems[1] related to naturally occurring alkaloids. Thus, the indole isosteres of dihydrothebainone[4] and argemonine (N-methylpavine)[1] as well as an indoline analog in the aporphine series[5] have been prepared.

Our observation[1] of the relatively mild conditions required for the rearrangement of 2-alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines to 2-alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium salts suggests that compounds derived from the latter may be considered as examples of another type of biologically feasible alternate precursor. Insertion of a 3-(indol-3-ylmethyl)isoquinoline derivative such as **2** at some stage of a biogenetic-type synthesis would be expected to give rise to new types of alkaloidal systems. The present investigation concerns the use of **2** as a precursor in a synthetic scheme, analogous to that employed[4] in the preparation of the indole isostere of dihydrothebainone. The resulting products, the epimeric ketones **7a** and **7b**, are representative of the previously unreported cyclohex[*d*]indolo[2,3-*f*]morphan ring system.[6,7]

Precursor **2** was prepared by reduction of **1** as described previously.[1] While **2** itself could be used as a starting material for the synthetic sequence (Chart I), it was found most convenient to subject **1** directly to the conditions of Birch reduction. The resulting hexahydroisoquinoline **3** was refluxed with aqueous methanolic hydrochloric acid to give the epimeric unsaturated ketones **5**. These were not isolated, since they cyclized, under the reaction conditions, to give a mixture of the epimeric cyclic ketones **7a** and **7b**.[8] The major product, isolated in 48% yield, had a higher melting point (260–262°), a lower solubility in chloroform and methanol, and a slower migration rate on thin layer chromatography than the minor product (mp 227.5–228.5°), which was isolated in 12% yield.[9] Both compounds gave a negative Ehrlich test and ultraviolet spectra which were typical of 2,3-dialkylindoles.

The configuration of the higher melting ketone was established as that of **7a** by examination of the NH frequencies of the alcohols **9a** and **10a** produced, respectively, by lithium aluminum hydride reduction and reaction with phenyllithium. Dreiding models indicate that, in the chair conformation of **9a** and **10a** with the axial hydroxyl, there should be strong intramolecular bonding between the oxygen and the indole

(1) Paper IV in this series: H. Zinnes, F. R. Zuleski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 3605 (1968).

(2) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *ibid.*, **32**, 2551 (1967).

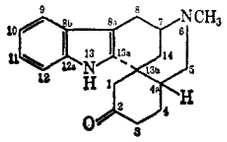
(3) E. E. van Tamelen, "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zeckmeister, Ed., Springer-Verlag, Vienna, Austria, 1961, p 242.

(4) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(5) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *ibid.*, **33**, 1663 (1968).

(6) The numbering system (see Chart I) was chosen to conform as closely as possible with that used for the cyclohex[*j*]indolo[2,3-*f*]morphan series.[2] Compounds **7a** and **7b** differ only in the ring junction at C-4. In **7a**, the hydrogen at C-4 is *trans* with respect to the indole group at C-5, so that the geometry of the ring system resembles that of a *trans*-decahydroisoquinoline (see structure **9a**). The geometry of **7b** resembles that of a *cis*-decahydroisoquinoline (see structure **9b**), the hydrogen at C-4 being *cis* to the indole at C-5. Thus, **7a** is referred to as the *trans* epimer and **7b** as the *cis* epimer. In naming compounds of the **a** series, the prefix "*trans*-[5(indolo),4H]" is used, whereas "*cis*-[5(indolo),4H]" is used for the **b** series. The geometry of the *trans* epimer (**a** series) most closely resembles that of the compounds known as *cis*-morphinans (including morphine) since the latter also contain a *trans*-decahydrosioquinoline moiety. This apparent discrepancy arises from the fact that in the morphinans, ring E is fused with both ring C and ring D; the conventional stereochemical designation of the series was apparently chosen with reference to the CE ring fusion. In **7**, the only fusion of ring E is with ring D.

(7) The systematic name for **7a** is *trans*-[13b(indolo),4aH]1,2,3,4,4a,5,6,-7,8,13-decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-one, with the numbering as follows.

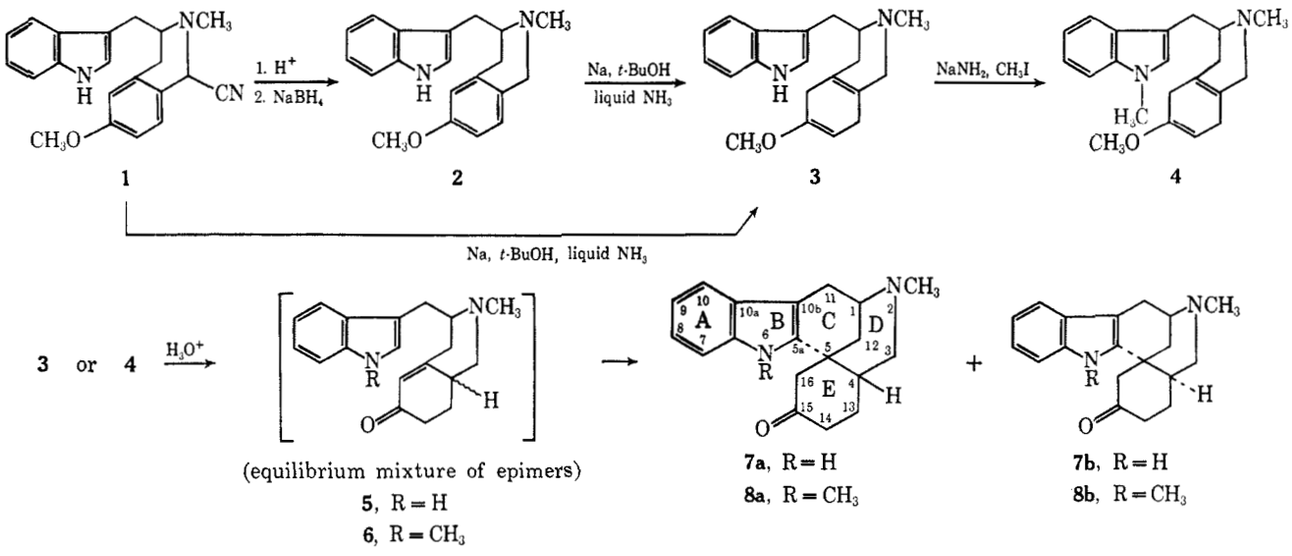


It differs from its *cis* epimer in the configuration at C-4a.

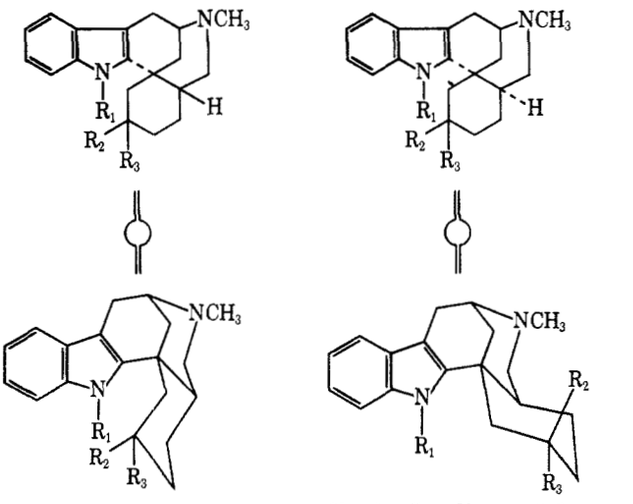
(8) Thin layer chromatograms suggested approximately a 70:30 mixture.

(9) Another 18% was isolated as a crystalline mixture of the two ketones.

CHART I



hydrogen; no such interaction exists in **9b** or **10b**. Dichloromethane solutions of **9a** and **10a** showed hydrogen-bonded NH absorption at 3260 and 3300 cm^{-1}, respectively, whereas the corresponding alcohols **9b** and **10b**, derived from the lower melting ketone, showed normal absorption at 3480 cm^{-1}.



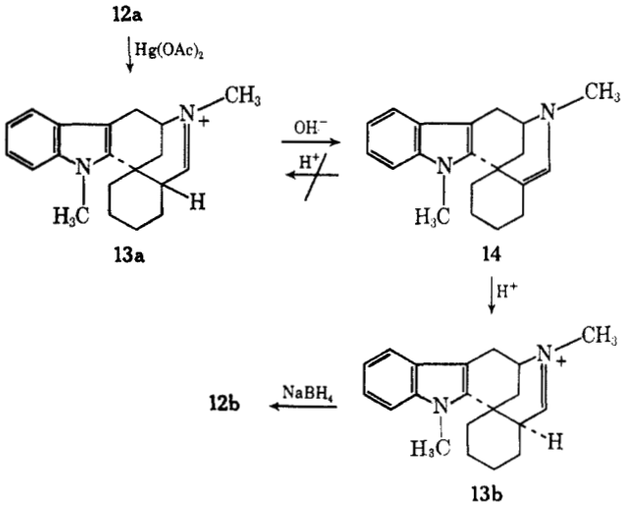
9a, $R_1 = R_3 = H$, $R_2 = OH$ **9b**, $R_1 = R_3 = H$, $R_2 = OH$
10a, $R_1 = H$, $R_2 = OH$, $R_3 = C_6H_5$ **10b**, $R_1 = H$, $R_2 = OH$, $R_3 = C_6H_5$
11a, $R_1 = R_2 = R_3 = H$ **11b**, $R_1 = R_2 = R_3 = H$
12a, $R_1 = CH_3$, $R_2 = R_3 = H$ **12b**, $R_1 = CH_3$, $R_2 = R_3 = H$

Wolff–Kishner reduction of **7a** and **7b** took place readily to give **11a** and **11b**, respectively. Examination of a model of the chair form of **11a** shows a considerable interaction between a hydrogen at C-15 and the indole NH. In the case of the derivative **12a**, the N_{Ind}-methyl group and a C-15 hydrogen practically overlap, so that it is unlikely that this compound could exist in an all-chair conformation. These interactions are absent in **11b** and its N_{Ind}-methyl derivative **12b**.

As expected, the reaction of **11b** (derived from the lower melting ketone) with sodium amide and methyl iodide in liquid ammonia proceeded smoothly and completely to give **12b**. When **11a** (derived from the higher melting ketone) was subjected to the same conditions, less than 25% conversion took place and **12a** could not be isolated. This slower rate of alkylation of **11a** relative to that of **11b** is further evidence that the higher melting ketone is the *trans* epimer **7a** and the lower melting ketone the *cis* epimer **7b**. Compound **12a** was ultimately prepared in 43% yield by prolonged refluxing of **11a** with an excess of sodium hydride and dimethyl carbonate in tetrahydrofuran.[10]

That the two series were indeed epimeric at C-4 was established experimentally by conversion of **12a** to **12b**, as depicted in Chart II. Compound **12a** was

CHART II



oxidized by heating with mercuric acetate in acetic acid.[11] The resulting immonium salt **13a** was treated with alkali to cause shifting of the double bond to give **14**, thus destroying the asymmetric center at C-4. Conversion of **14** to the salt **13b** followed by sodium borohydride reduction yielded a product whose major component was identified as **12b**. Thin layer chromatograms indicated the presence of an unidentified, faster moving impurity, but the slower spot characteristic of **12a** was completely absent. The essentially

(10) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **8**, 200 (1965).

(11) N. J. Leonard and F. P. Hauch, Jr., *J. Amer. Chem. Soc.*, **79**, 5279 (1957).

complete epimerization of **12a** to **12b** is understandable in view of the severe interaction between the N-methyl and a C-15 hydrogen, which would tend to inhibit formation of **13a** on acidification of **14**.

The results of the latter experiment suggested that we might achieve stereoselective cyclization to the *cis* epimer **8b** (Chart I) if we started with the N_{Ind}-methyl derivative **6**. Though not so severe as in **12a**, the steric interaction between the N_{Ind}-methyl and the C-15 substituent (carbonyl) of **8a** appears considerable. In order to explore the possibility that this interaction might be sufficient to retard the formation of **8a**, we prepared the N_{Ind}-methylhexahydroisoquinoline **4** by treating **3** with sodium amide and methyl iodide in liquid ammonia. However, the product obtained on refluxing **6** with acid was the same type of epimeric mixture (**8a** and **8b**) as was obtained from **5**, with the major component being the *trans* epimer **8a**. Thus, it appears that the aforementioned steric interaction is insufficient, when C-15 is trigonal, to alter the normal course of the cyclization.[12]

The identity of **8b** was established by refluxing it with potassium hydroxide and hydrazine in ethylene glycol to give **12b** in 73% yield. Under the same conditions, **8a** gave a mixture from which **12a** could be isolated in only 13% yield. The difficulty encountered in carrying out the Wolff–Kishner reduction of **8a** is evidently another reflection of the unfavorable steric interaction existing in **12a**. Still further evidence for our configurational assignment is given by the nmr spectra, which indicate greater shielding of the N_{Ind}-methyl hydrogens of **8a** relative to those of **8b**, **12a**, and **12b**.[13]

Experimental Section[14,15]

3-(Indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4,5,8-hexahydroisoquinoline (3). A. Preparation from 1.—A solution of 20 g of **1**[1] in 340 ml of tetrahydrofuran was added to 680 ml of liquid ammonia, and 30 g of sodium and 127 ml of *t*-butyl alcohol were alternately added in portions over a period of 1 hr. The solution was stirred at reflux for 1 hr and the blue color was discharged by the addition of 120 ml of *t*-butyl alcohol. The ammonia was evaporated off and the tetrahydrofuran solution was poured into 3500 ml of ice–water. The resulting precipitate was collected and triturated with ethanol to give 16 g of crystalline product, mp 167–169° dec. Recrystallization of a portion from benzene gave pure **3**: mp 168–169° dec; ir ν_{max}^{Nujol} 3100 (m), 1710 (w), and 1668 cm^{-1} (m), absence of the strong band at 1615 cm^{-1} which is present in **2**.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.79; H, 7.97; N, 9.27.

B. Preparation from 2.—To a mixture of 66 ml of liquid ammonia and 2.5 ml of water was added a solution of 1.0 g of **2**[1] in 33 ml of tetrahydrofuran. This was followed by treatment with 4.5 g of sodium and 7 ml of *t*-butyl alcohol, added alternately in portions over a 1-hr period. The solution was stirred at reflux for 1 hr and the blue color was discharged by the addition of 5 ml of *t*-butyl alcohol. The ammonia was evaporated off, the tetrahydrofuran solution was poured into 1000 ml of water, and the resulting mixture was extracted with dichloromethane. Evaporation of the solvent and trituration of the residue with ethanol gave 0.8 g of crystalline material, mp 260–262° dec; the ir spectrum was identical with that of the product described in A, above. Recrystallization from benzene gave 0.5 g of product, mp 165–167° dec. Recrystallization from acetonitrile raised the melting point to 167–168° dec.

***trans*- and *cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ones (7a and 7b).**—A mixture of 43 g of **3**, 310 ml of concentrated hydrochloric acid, and 750 ml of methanol was refluxed under nitrogen for 1 hr, the methanol was distilled off, and 2000 ml of water was added. The mixture was made alkaline with ammonium hydroxide and extracted with dichloromethane. Concentration of the dried dichloromethane solution to a volume of *ca.* 100 ml gave 20.1 g of chromatographically pure (R_f 0.11) **7a**, mp 259–261° dec, which gave a negative Ehrlich test. Recrystallization from methanol gave analytical material: mp 260–262°; ir ν_{max} 3480 (s, NH) and 1706 cm^{-1} (s, C=O); uv λ_{max} 225 (ϵ 36,500), 282 (ϵ 8000), and 290 mμ (ϵ 7000).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.28; H, 7.72; N, 9.63.

The phosphate salt, which precipitated when a methanol–dichloromethane solution of the base was treated with a slight excess of phosphoric acid, had mp 294–296° dec.

Anal. Calcd for $C_{19}H_{22}N_2O \cdot H_3PO_4 \cdot {}^1/_2CH_3OH$: C, 57.35; H, 6.66; N, 6.86; P, 7.58. Found: C, 57.36; H, 6.47; N, 6.85; P, 7.36.

The hemimethanolate was stable to drying *in vacuo* at 140°.

Recrystallization from water gave the hemihydrate, mp 290–296° dec.

Anal. Calcd for $C_{19}H_{22}N_2O \cdot H_3PO_4 \cdot {}^1/_2H_2O$: C, 56.86; H, 6.53; N, 6.98; P, 7.72; H_2O, 2.2. Found: C, 56.85; H, 6.74; N, 7.08; P, 7.44; H_2O (by Karl Fischer), 2.9.

The dichloromethane mother liquor was concentrated to a small volume and chromatographed over 430 g of alumina (column height 48 cm), using dichloromethane as the eluent. The first 2000 ml of eluate was found to contain a mixture of **7a** and the faster-moving (R_f 0.31) **7b**, the former being the major component. Evaporation of the next 10 l. of eluent gave 8.5 g of a solid consisting predominately of **7b**. Recrystallization from acetonitrile–dichloromethane gave 4.8 g of chromatographically pure **7b**, mp 225–226.5° dec, which gave a negative Ehrlich test. Recrystallization from acetonitrile gave analytical material: mp 227.5–228.5° dec; ir ν_{max} 3480 (s, NH) and 1714 cm^{-1} (s, C=O); uv λ_{max} 225 (ϵ 36,400), 283 (ϵ 8250), and 290 mμ (ϵ 7600).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.74; H, 7.67; N, 9.80.

***trans*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (9a).**—A mixture of 1.0 g (0.003 mol) of **7a**, 1.0 g (0.026 mol) of lithium aluminum hydride, and 150 ml of tetrahydrofuran was stirred at room temperature for 20 hr, hydrolyzed, and filtered. Evaporation of the filtrate gave a solid residue which was triturated with ethyl acetate and then recrystallized from the same solvent to give 0.5 g of crystalline product: mp 218–220° dec; ir ν_{max} (2.5, 0.625, and 0.31% in CH_2Cl_2) 3600 (m, OH) and 3260 cm^{-1} (s, NH).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.71; H, 8.18; N, 9.19.

***cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2] benzazocin-2-ol (9b).**—The same conditions were employed with 1.0 g (0.003 mol) of **7b**. Evaporation of the tetrahydrofuran filtrate gave a solid residue which was triturated with acetonitrile to give 0.86 g of crystalline product, mp 275–277° dec (darkens at 260°). Recrystallization from acetonitrile–dichloromethane gave 0.45 g of material: mp 275–277° dec (darkens at 260°); ir ν_{max} (0.31% in CH_2Cl_2) 3600 (m, OH) and 3480 cm^{-1} (s, NH).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.19; H, 8.14; N, 9.65.

(12) In the case of *cis* epimer formation, attack of the indole perpendicular to the plane of the carbonyl requires that ring D have the boat conformation in the transition state. Formation of the *trans* epimer is favored because the required perpendicular attack can occur in a transition state having ring D in the chair form. See L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

(13) See Experimental Section. A Dreiding model of **8a** shows the N_{Ind}-methyl to lie above the plane of the carbonyl group.

(14) Systematic names of compounds are used in the titles of the experiments. See ref 7.

(15) Melting points were determined using the Thomas–Hoover capillary melting point apparatus, which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. The former were determined as solutions in 95% ethanol and the latter, unless otherwise stated, as chloroform solutions. The nmr spectra were determined in $CDCl_3$ with the Varian A-60 spectrometer using Me_4Si as an internal standard. Thin layer chromatography was carried out on Brinkmann aluminum oxide (type 1) precoated glass plates using a mixture of *n*-heptane and 2-butanone (1:3) as the eluent. Chromatograms were developed with iodine. The drying agent used throughout was sodium sulfate.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-2-phenyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (10a).—To a mixture of 5 ml of 3 *M* ethereal phenylmagnesium bromide and 125 ml of tetrahydrofuran was added 0.59 g (0.002 mol) of **7a** in 25 ml of tetrahydrofuran. The mixture was refluxed for 6 hr, poured into excess aqueous ammonium chloride solution, and extracted with dichloromethane. The gummy extract was triturated with methanol to give 0.39 g of product, mp 265–270° dec (darkens at 245°). Recrystallization from methanol–dichloromethane gave 0.20 g of an analytical sample: mp 270–273° dec (darkens at 260°); ir ν_{max} (0.3 and 0.15% in CH_2Cl_2) 3550 (m, OH) and 3300 cm^{-1} (s, NH).

Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.41; H, 7.72; N, 7.70.

cis-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-2-phenyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (10b).—The same conditions were employed with 0.59 g (0.002 mol) of **7b**. Trituration of the gummy extract with methanol gave 0.39 g of product, mp 235–240° dec. Recrystallization from methanol–dichloromethane gave 0.25 g of an analytical sample: mp 241–242° dec; ir ν_{max} (0.3 and 0.15% in CH_2Cl_2) 3570 (m, OH) and 3480 cm^{-1} (s, NH).

Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.35; H, 7.40; N, 7.38.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (11a).—A mixture of 13.6 g (0.046 mol) of **7a**, 136 g of hydrazine hydrate, 13.6 g of sodium hydroxide, and 820 ml of ethylene glycol was refluxed under nitrogen for 1 hr and distilled at atmospheric pressure until the reflux temperature was a constant 194°. Additional ethylene glycol was added to replace that lost in the distillation, and refluxing was continued for 3 hr. The reaction mixture was concentrated to half of its volume and poured into 2800 ml of ice–water. The precipitated solid was collected, washed well with water, and dissolved in dichloromethane. The dried solution was evaporated to a residue which was triturated with methanol to give 10.3 g of product, mp 142–145°. Recrystallization from methanol gave analytical material: mp 144–145°; ir ν_{max} 3480 cm^{-1} (s, NH); uv λ_{max} 227 (ϵ 36,000), 282 (ϵ 7400), and 289 mμ (ϵ 6500).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.57; H, 8.77; N, 9.91.

cis-[13b(Indolo)4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (11b).—The above conditions were employed with 2.0 g (0.066 mol) of **7b**, 20 g of hydrazine hydrate, 2 g of sodium hydroxide, and 125 ml of ethylene glycol. The dried dichloromethane solution was evaporated to a residue which was triturated with 5 ml of methanol to give 1.5 g of crystalline product, mp 130.5–132°. Recrystallization from methanol–dichloromethane gave 1.3 g of analytical material: mp 132.5–133.5°; ir ν_{max} 3480 cm^{-1} (s, NH); λ_{max} 227 (ϵ 37,000), 282 (ϵ 7600), and 290 (ϵ 6800).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.40; H, 8.60; N, 10.28.

cis-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (12b).—To a solution of 0.36 g (0.0092 mol) of sodium amide in 50 ml of liquid ammonia was added 0.65 g (0.0023 mol) of **11b**. The mixture was stirred for 1 hr, 0.84 ml (0.0138 mol) or methyl iodide was added, and stirring was continued for 3 hr. Evaporation of the ammonia followed by the addition of ice–water gave a precipitate which was collected and dissolved in dichloromethane. Evaporation of the dried solution gave 0.56 g of solid residue which was devoid of NH absorption. Trituration with methanol gave 0.465 g of crystalline product: mp 125–126.5°; uv λ_{max} 231 (ϵ 36,000), 286 (ϵ 7600), and 293 mμ (ϵ 7300); nmr δ 3.85 (3 H, N_{Ind}-methyl) and 2.32 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.60; H, 8.90; N, 9.51. Found: C, 81.50; H, 8.77; N, 9.69.

Attempted Alkylation of 11a by $NaNH_2$ and CH_3I in Liquid Ammonia.—The quantities, reaction conditions, and work-up procedure were *exactly* the same as those described above for the corresponding reaction with **11b**. Evaporation of the dried dichloromethane solution gave a semisolid which was triturated with methanol to give 0.57 g of a solid, mp 119–124°. The infrared spectrum showed a strong NH band at 3480 cm^{-1}. The nmr spectrum showed a N_{Ind}-methyl signal at 3.90 ppm which integrated for only 25% of the theoretical value for **12a**.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (12a).—A mixture of 4.0 g (0.014 mol) of **11a**, 1.8 g (0.042 mol) of a 55% mineral oil dispersion of sodium hydride, 6.3 g (0.07 mol) of dimethyl carbonate, and 150 ml of tetrahydrofuran was refluxed with stirring for 96 hr. The tetrahydrofuran was evaporated off, the residue was stirred with ice–water, and the mixture was made acidic by the addition of dilute hydrochloric acid. It was then made basic with sodium bicarbonate solution and extracted with ether. The ether solution was washed well with water, dried, and evaporated. The residue (4 g) was chromatographed over 120 g of alumina using ether as the eluent. Evaporation of the eluate gave a residue which was devoid of NH absorption. Recrystallization from Skellysolve B gave 1.8 g of product, mp 122–124°. Another recrystallization gave an analytical sample: mp 123–124°; uv λ_{max} 231 (ϵ 35,000), 285 (ϵ 7500), and 293 mμ (ϵ7100); nmr δ 3.90 (3 H, N_{Ind}-methyl) and 2.40 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.60; H, 8.90; N, 9.51. Found: C, 81.84; H, 8.88; N, 9.48.

Epimerization of 12a to 12b.—A mixture of 1.7 g of **12a**, 10 g of mercuric acetate, and 100 ml of 10% acetic acid was heated on a steam bath for 4 hr and the precipitated mercurous acetate was filtered off. The filtrate was heated to boiling and treated with 1 ml of 10% hydrochloric acid, and then hydrogen sulfide was bubbled through. The mixture was filtered through supercel, the dark filter cake being washed well with 10% acetic acid. The clear yellow filtrate (containing **13a**) was made alkaline with sodium hydroxide and the resulting precipitate was collected and dissolved in dichloromethane. The dichloromethane solution was washed well with water, dried, and evaporated. Most of the residue dissolved in petroleum ether (bp 30–40°), leaving a small amount of dark insoluble material which was removed by filtration. Dilution of the filtrate (containing **14**) with ether, followed by the addition of ethereal hydrogen chloride, gave a precipitate (**13b**) which was collected and washed well with ether. It was dissolved in 25 ml of ethanol, 1 g of sodium borohydride was added, and the mixture was stirred at room temperature for 4 hr. Addition of 600 ml of water followed by extraction with dichloromethane and evaporation of the latter solvent gave 1.2 g of a solid residue; thin layer chromatograms indicated a major component (R_f 0.44) which corresponded to **12b** and a minor, faster-moving (R_f 0.60) component; the spot (R_f 0.28) corresponding to **12a** was completely absent. Recrystallization from acetonitrile gave 700 mg of crystalline material, mp 123–126°, which still showed a trace of the faster moving component. Another recrystallization gave 450 mg of **12b**, mp 127–128°, identified by mixture melting point and comparison of its infrared spectrum with that of a sample prepared by alkylation of **11b**.

trans- and *cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ones (8a and 8b).—To a solution of 6.4 g (0.165 mol) of sodium amide in 800 ml of liquid ammonia was added 17.0 g (0.55 mol) of **3**. The mixture was stirred for 1.5 hr, 31.2 g (0.22 mol) of methyl iodide was added, and stirring was continued for 2.5 hr. Evaporation of the ammonia followed by addition of ice–water gave a crystalline precipitate (**4**) which was collected, washed well with water, and sucked dry. This was not purified further but was refluxed with a mixture of 300 ml of methanol and 120 ml of concentrated aqueous hydrochloric acid, under a nitrogen atmosphere, for 2 hr. The methanol was distilled off, and the residue was partitioned between dilute aqueous ammonium hydroxide and dichloromethane. Concentration of the dried dichloromethane solution to a small volume gave 5.6 g of crystalline material. The remainder of the dichloromethane was evaporated and the residue was triturated with 10 ml of methanol to give 2.8 g of additional crystals. These products were combined and recrystallized from methanol–dichloromethane to give 6.7 g of chromatographically pure (R_f 0.15) **8a**: mp 210–212° dec; ir ν_{max} 1704 cm^{-1} (s, C=O); uv λ_{max} 228 (ϵ 36,000), 285 (ϵ 7850), and 294 mμ (ϵ 7700); nmr δ 3.55 (3 H, N_{Ind}-methyl) and 2.47 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.77; H, 7.86; N, 9.33.

The methanol filtrate was evaporated to dryness and the residue was dissolved in dichloromethane and chromatographed over 210 g (34-cm column) of alumina using dichloromethane as the eluent. The first 150 ml of eluate was discarded, and the next 1500 ml was evaporated to dryness. The residue (4.7 g) was recrystallized from Skellysolve B to give 1.75 g of chromatographically pure (R_f 0.38) **8b**: mp 161–162°; ir ν_{max} 1708 cm^{-1} (s, C=O);

uv λ_{max} 229 (ε 37,000), 286 (ε 8300), and 294 mμ (ε 7700); nmr δ 3.85 (3 H, N_{Ind}-methyl) and 2.32 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.91; H, 7.94; N, 9.18.

Wolff–Kishner Reduction of 8b.—A mixture of 1.0 g (0.00325 mol) of **8b**, 9.2 g of hydrazine hydrate, 1.0 g of sodium hydroxide, and 55 ml of ethylene glycol was refluxed under nitrogen for 1 hr and distilled at atmospheric pressure until the reflux temperature was a constant 194°. Additional ethylene glycol was added to replace that lost in the distillation and refluxing was continued for 2.5 hr. The reaction mixture was concentrated by distillation until crystals started to separate and was poured into 500 ml of ice–water. The precipitated solid was collected, washed well with water, and dissolved in dichloromethane. Evaporation of the dried solution gave 900 mg of a solid residue which showed a single spot (R_f 0.44) on thin layer chromatography. Recrystallization from acetonitrile gave 700 mg of **12b**, mp 127–128°, identified by mixture melting point, thin layer chromatography, and infrared spectrum.

Wolff–Kishner Reduction of 8a.—A Wolff–Kishner reduction was carried out with 3.2 g (0.01 mol) of **8a**, using *exactly* the same conditions described above. The precipitate which separated on pouring the reaction mixture into water was dissolved in dichloromethane. The solution was washed well with water, dried, and evaporated to an oily residue. This was chromatographed over 60 g of alumina, using dichloromethane as the eluent. Evaporation of the first 1000 ml of eluate gave 900 mg of a crystalline residue which could be shown by chromatography to consist of a mixture of the expected product together with some faster moving material. Recrystallization from Skellysolve B gave 400 mg of **12a**, mp 121–123°, which showed a single spot (R_f 0.28) on thin layer chromatography. Recrystallization gave material, mp 123–124°, which was identified as **12a** by mixture melting point, thin layer chromatography, and comparison of infrared spectra.

Registry No.—**2**, 16957-67-8; **3**, 21369-44-8; **7a**, 21369-45-9; **7a** (phosphate salt), 21369-46-0; **7b**, 21369-47-1; **7b** (phosphate salt), 21369-48-2; **8a**, 21372-16-7; **8b**, 21372-17-8; **9a**, 21372-18-9; **9b**, 21372-19-0; **10a**, 21372-20-3; **10b**, 21372-21-4; **11a**, 21372-22-5; **11b**, 21372-23-6; **12a**, 21372-24-7; **12b**, 21372-25-8.

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Substituted γ-Pyrans[1]

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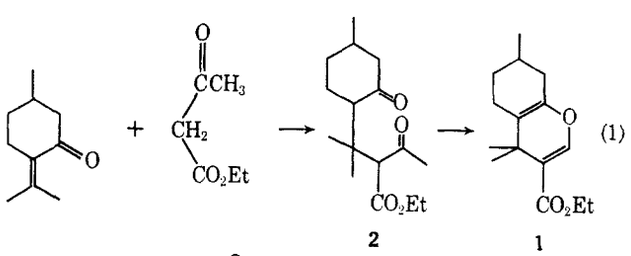
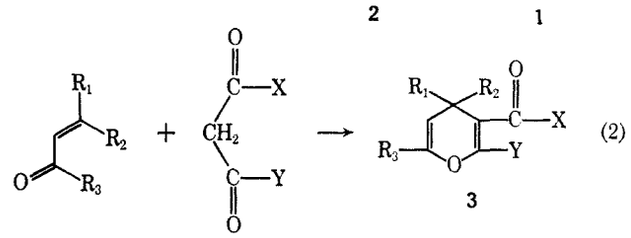
A general route to substituted γ-pyran derivatives involving the zinc chloride catalyzed condensation of β-dicarbonyl compounds with aldehydes or α,β-unsaturated ketones and aldehydes is described. For example, ethyl acetoacetate reacts with formaldehyde to give 3,5-dicarboethoxy-2,6-dimethyl-4H-pyran, and with mesityl oxide to give 3-carboethoxy-2,4,4,6-tetramethyl-4H-pyran. Chemical and spectral properties of these γ-pyran derivatives are described.

γ-Diketones are readily converted by acid into resonance stabilized furan derivatives,[2] while δ-diketones, when subjected to similar conditions, are generally assumed to undergo intramolecular aldol cyclization to cyclohexenone derivatives.[3] γ-Pyran derivatives have only been obtained in cases where structural features, such as the lack of an enolizable hydrogen[4] or improper geometric relationships,[5] prohibit the formation of cyclohexenone derivatives. The formation of γ-pyran (**1**)[6] in the zinc chloride catalyzed reaction of pulegone with ethyl acetoacetate (eq 1) under conditions which minimize the reconversion of pyran **1** to the intermediate δ-diketone **2** suggests that the cyclization of δ-diketones to γ-pyrans might be a general reaction which has been long overlooked. We have in fact found that the condensation of α,β-unsaturated aldehydes and ketones with β-dicarbonyl compounds provides a general route to substituted γ-pyran derivatives (eq 2).



(1)



(2)

$R_1 = R_2 = R_3 = CH_3$

a, X = OEt, Y = CH_3

b, X = OCH_3, Y = CH_3

c, X = Y = CH_3

d, Y = C_6H_5, X = OEt

Mesityl oxide condenses with ethyl or methyl acetoacetate, 2,4-pentandione, and ethyl benzoyl acetate to give γ-pyrans **3a**, **b**, **c**, and **d**, respectively. Although the yields are relatively low, 10–25%, the ready availability of the starting material and the lack of an alternate route to these compounds makes this an attractive synthetic procedure.

(1) Based on the thesis submitted by H. S. H. in partial fulfillment of the requirements for the Ph.D. degree from Purdue University, Jan 1969.

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