A Novel Transannular Ring Contraction from the Attempted Wolff–Kishner Reduction of 2,7-Diphenylhexahydro-4-azepinone[1]

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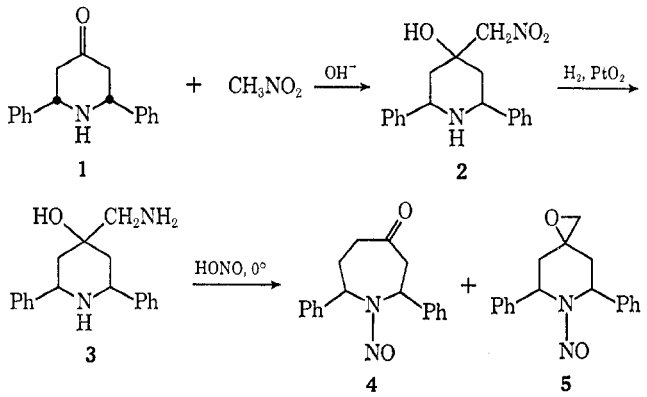
The synthesis of 2,7-diphenylhexahydro-4-azepinone (**8**) from a Tiffeneau–Demajanov ring expansion is reported. The formation of 2,7-diphenylhexahydroazepine is also described. An unusual transannular rearrangement occurs during the attempted Wolff–Kishner reduction of 2,7-diphenylhexahydro-4-azepinone to give 2-phenyl-5-(β-phenethyl)pyrrole. The structure of the pyrrole was proven by alternate synthesis. A possible mechanism for the ring contraction is suggested.

As part of our investigations of the fragmentation of asymmetrically substituted benzylic hydrazines and N-nitrosoamines, the synthesis of 2,7-diphenylhexahydroazepine (**10**) was undertaken.

The ready availability of 2,6-diphenyl-4-piperidone (**1**) from the condensation of acetone, benzaldehyde, and ammonium acetate[3] suggested a Tiffenau–Demajanov ring enlargement as an easy route to the hexahydroazepine system. The condensation of **1** with nitromethane under basic conditions gave 2,6-diphenyl-4-(nitromethyl)-4-piperidinol (**2**) in 60% yield. Compound **2** was reduced catalytically in 92% yield to 2,6-diphenyl-4-(aminomethyl)-4-piperidinol (**3**). Treatment of **3** with nitrous acid at low temperatures gave two compounds, **4** and **5** (Scheme I).

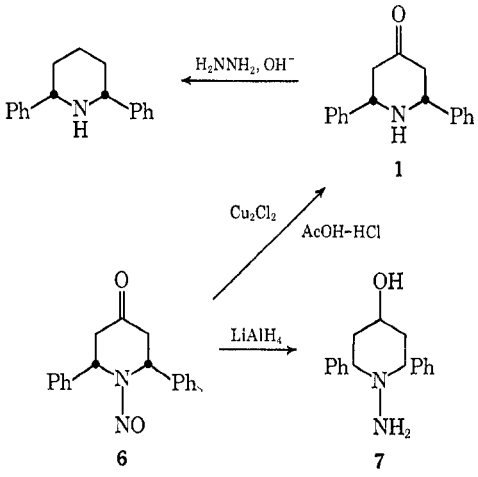
SCHEME I



The assigned structures **4** and **5** are supported by the results of the elemental analyses of the compounds and their infrared spectra. Both compounds gave a positive Lieberman nitroso test. Compound **4** had a strong absorption at 1450 cm^{-1} which was assigned to the >N—N=O system. In contrast, **5** (6-nitroso-5,7-diphenyl-1-oxa-6-azaspiro[2.5]octane) showed no absorption in the carbonyl region and had a strong band at 1430 cm^{-1} (>N—N=O) and medium-intensity peaks at 1250, 890, and 835 cm^{-1} (epoxy group).

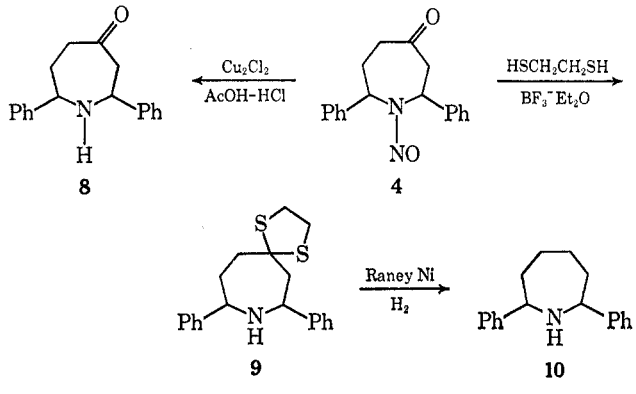
Trial experiments carried out with *cis*-N-nitroso-2,6-diphenyl-4-piperidone (**6**) indicated that reduction of the C=O bond to a methylene group[4] could be accomplished readily only after removal of the N-nitroso group. Cuprous chloride in a glacial acetic acid–hydrochloric acid mixture converted **6** into *cis*-**1**. The lithium aluminum hydride reduction of **6** gave the hydrazino alcohol (**7**) in 76% yield (Scheme II).

SCHEME II



The denitrosation of **4** with cuprous chloride gave a 35% yield of analytically pure 2,7-diphenylhexahydro-4-azepinone (**8**). Conversion of **8** into the ethylene thioketal derivative (**9**) and reductive desulfurization gave 2,7-diphenylhexahydroazepine (**10**, Scheme III). Although in one case a 36% yield of **10** was realized with Raney nickel W-7 grade catalyst which had been stored in the refrigerator for 2 months, further experiments (in different solvents with various catalysts and at different temperatures) indicated that the yields of this reduction were erratic. The Wolff–Kishner reduction of **8** was investigated next as a possible alternative to the reductive desulfurization.

SCHEME III



(1) This is the 47th in a series of papers. For the previous contribution, see C. G. Overberger, J. W. Stoddard, C. Yaroslavsky, H. Katz, and J.-P. Anselme, *J. Amer. Chem. Soc.*, **91**, 3226 (1969).

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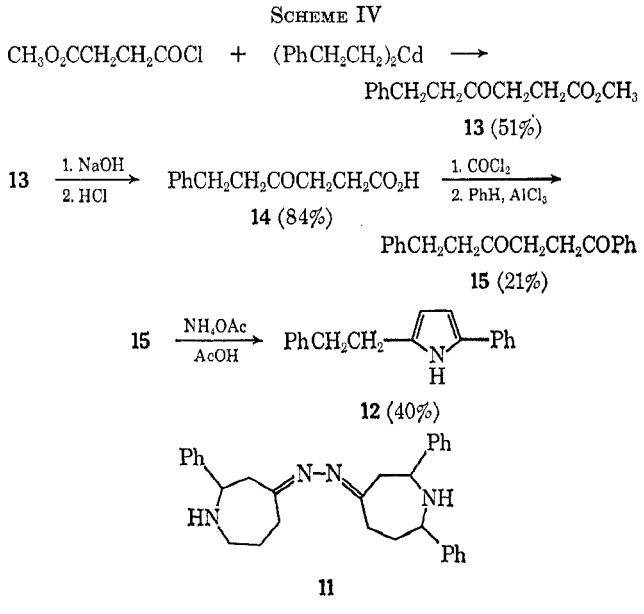
(3) V. Baliah, A. Ekambaram, and T. S. Govindarajan, *Curr. Sci.* (India), **23**, 264 (1954).

(4) V. Baliah and A. Ekambaram, *J. Indian Chem. Soc.*, **32**, 274 (1955).

The modification of the Wolff–Kishner reduction reported by Grundon, Henbest, and Scott[5] gave what apparently is the corresponding azine (**11**). The Huang-Minlon procedure resulted in the formation of a compound, $C_{18}H_{17}N$, in 87% yield. It gave an immediate and intense red coloration with *p*-dimethylaminobenzaldehyde in concentrated hydrochloric acid (Erlich reaction) which suggested the presence of a pyrrole. Its infrared spectrum exhibited a strong band at 3450 cm^{-1} (NH) and peaks at 1590, 1480, and 1450 cm^{-1}, consistent with the pyrrole structure. Its ultraviolet spectrum had a band at 300 mμ (ϵ 29,000), with a shoulder at 225 mμ (ϵ 19,100). The nmr spectrum indicated the presence of ten aromatic hydrogens at τ 2.91, two vinylic hydrogens at τ 3.71 and 4.1, and four methylenic hydrogens at τ 7.05. These data suggested 2-phenyl-5-(β-phenethyl)pyrrole (**12**) as the structure of the compound. Confirmation of this structure was provided by the preparation of authentic **12**, as shown in Scheme IV. The thioketal **9** also gave

SCHEME IV



12 with hydrazine under conditions closely similar to those of the Huang-Minlon[6] procedure.

The formation of **12** from the hydrazone of **4** under basic conditions is apparently the result of an unusual transannular rearrangement, examples of which have not been previously reported in the literature. In order for the pyrrole structure with the β-phenylethyl side chain in the 2 position to be formed, the N–C_α bond of the hexahydroazepinone must be cleaved. If the initial step of the Wolff–Kishner reduction occurs normally, then a nucleophilic displacement on the ring nitrogen would produce the required cleavage. Although nucleophilic displacements on nitrogen are rare and difficult, the favorable conformation may explain its occurrence in this case.[7]

Once the ring contraction has taken place, the conversion into the final product would proceed as shown in Scheme V.

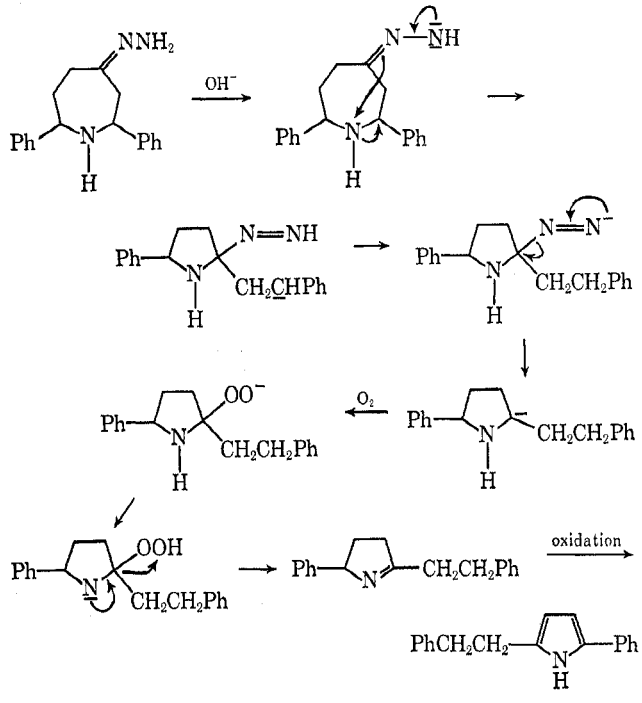
(5) M. F. Grundon, H. B. Henbest, and M. D. Scott, *J. Chem. Soc.*, 1855 (1963).

(6) V. Georgian, R. Harrison, and N. Gubish, *J. Amer. Chem. Soc.*, **81**, 5834 (1959).

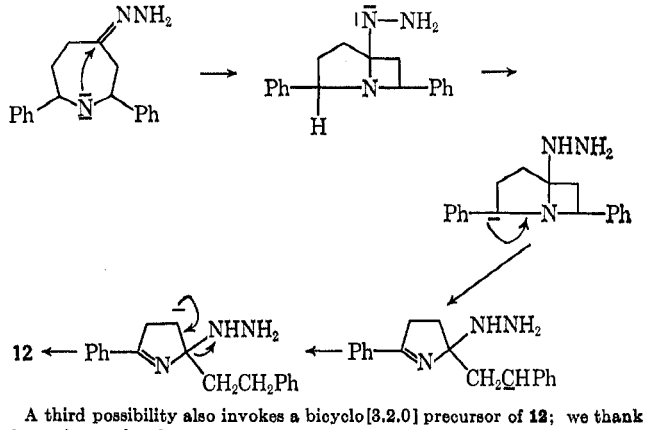
Experimental Section[8]

2,6-Diphenyl-4-nitromethyl-4-piperidinol (2).—A hot ethanol solution (150 ml) containing 25.5 g (0.10 mol) of 2,6-diphenyl-4-piperidone[3] and 8 g (0.13 mol) of nitromethane was added in a rapid stream to a warm, stirred solution of 2.3 g (0.1 g-atom) of

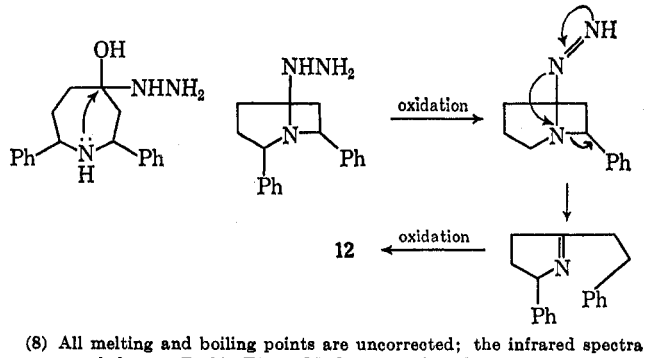
SCHEME V



(7) An alternative mechanism involving displacement on the >C=N— can be envisioned; this does not require the oxidation steps.



A third possibility also invokes a bicyclo[3.2.0] precursor of **12**; we thank the reviewers for these suggestions.



(8) All melting and boiling points are uncorrected; the infrared spectra were recorded on a Perkin-Elmer Model 521 infrared spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 350 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Model HR60 nmr spectrometer. Elemental analyses were provided by the Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

sodium in 100 ml of ethanol. The white, gelatinous mass was stirred for 3 hr and then allowed to stand overnight. To the stirred reaction mixture cooled in an ice bath, 12 ml of glacial acetic acid, followed by 100 ml of water, were added. Stirring was continued with cooling until the pasty mass became granular (4 hr). The solid was collected, washed with cold ethanol, and air dried. The yield of product was 22 g (71%), mp 153–158° dec. Two recrystallizations from ethanol gave an analytical sample, mp 175–177° dec.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.40; N, 8.97. Found: C, 69.40; H, 6.64; N, 8.77.

2,6-Diphenyl-4-aminomethyl-4-piperidinol (3).—To a solution of 15 g of 2,6-diphenyl-4-nitromethyl-4-piperidinol in 100 ml of glacial acetic acid was added 0.6 g of Adams platinum oxide. The reduction was carried out on a Parr hydrogenation apparatus at room temperature and 40 psi. After 1 hr the uptake of hydrogen virtually ceased. The catalyst was removed by filtration through Celite Filter-Aid. The combined filtrate and filter-cake washes were freeze dried. The residue was transferred to a funnel and washed with cold ethanol. The weight of the air-dried solid was 12.4 g (92%), mp 190–192° dec. Recrystallization from boiling ethanol did not change the melting point. The analytical sample was dried in an Abderhalden pistol over P_2O_5 at 100° (0.1 mm) for 3 hr.

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.59; H, 7.80; N, 9.93. Found: C, 76.44; H, 8.07; N, 10.20.

N-Nitroso-2,6-diphenyl-4-hexahydroazepinone (4).—To a cooled (ice bath), stirred suspension of 69 g (0.24 mol) of 2,6-diphenyl-4-aminomethyl-4-piperidinol in 75 ml of acetic acid and 500 ml of water was added over a period of 1 hr a solution of 69 g (1.0 mol) of sodium nitrite in 250 ml of water. Within 30 min, 150 ml of ether was added to facilitate stirring. The temperature during the addition was maintained at 10° or below. After the addition was completed, the mixture was allowed to stir overnight. The solid was then collected by filtration, washed with ether, and air dried. The crude product (17.1 g) was recrystallized from 350 ml of boiling ethanol, and gave 14.4 g (20%) of solid, mp 138–142°. An additional recrystallization from ethanol afforded an analytical sample, mp 139–140°.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.40; H, 6.12; N, 9.53. Found: C, 73.41; H, 6.24; N, 9.62.

A 2,4-dinitrophenylhydrazone derivative was prepared in the standard manner[9] and recrystallized from 2:1 ethyl acetate–ethanol, mp 224–226° dec.

Anal. Calcd for $C_{24}H_{22}N_6O_5$: C, 60.70; H, 4.64; N, 17.70. Found: C, 60.89; H, 4.71; N, 17.50.

Upon standing, the ether layer deposited 10.9 g (15%) of the epoxide **5**; it was collected and purified by repeated crystallization from ethanol, mp 126–128.5°.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.40; H, 6.12; N, 9.53. Found: C, 73.16; H, 6.36; N, 9.69.

In subsequent preparations of **4**, considerable quantities of **5** were present in the crude reaction product. Separation was accomplished either by continuous extraction with ether in a Soxhlet apparatus or by using Girard's reagent P.

N-Nitroso-2,6-diphenyl-4-piperidone (6).—To a cooled (ice bath), stirred suspension of 22.3 g (0.089 mol) of 2,6-diphenyl-4-piperidone in 200 ml of water, 50 ml of ethanol, and 9 ml of acetic acid was added a solution of 7 g of (0.11 mol) of sodium nitrite in 30 ml of water over a period of 15 min. Stirring was continued at 5° for 1 hr and at room temperature overnight. The crude solid was collected and washed with cold ethanol. The air-dried product was recrystallized from boiling ethanol and yielded 22 g (88%) of orange-tinged crystals, mp 107–108.5°. An analytical sample from ethanol had mp 108–109°.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.90; H, 5.72; N, 10.00. Found: C, 73.00; H, 5.77; N, 10.18.

The infrared spectrum showed N–NO bands at 1450, 1330, and 1175 cm^{-1}.

The relative configuration of the phenyl substituents in **6** is most probably that of the *cis* isomer. Baliah and Ekambaram[4] reported that Wolff–Kishner reduction of **1** gave *cis*-2,6-diphenylpiperidine, which was confirmed in the course of this work, and **1** was regenerated by denitrosation of **6**.

N-Amino-2,6-diphenyl-4-piperidinol (7).—A solution of 21.1 g (0.075 mol) of N-nitroso-2,6-diphenyl-4-piperidone in 150 ml of dry benzene was added over a period of 1.5 hr to a stirred suspension of 5.5 g (0.144 mol) of lithium aluminum hydride in 200 ml of anhydrous ether under a nitrogen atmosphere. After the addition was completed, the stirred reaction mixture was heated under reflux for 12 hr. The reaction mixture was then cooled to room temperature and hydrolyzed by the cautious addition of 20 ml of ethanol, 25 ml of water, and 20 ml of 30% aqueous sodium hydroxide, in the order given. The solvent was clarified by filtration and the residue was extracted with several portions of hot benzene. The solvent was then removed from the combined organic phase under reduced pressure. The residual oil was dissolved in 60 ml of chloroform, filtered, and treated with 160 ml of hexane. From the cooled solution, 15.3 g (76%) of white crystalline solid was obtained, mp 143–147°. Two recrystallizations from chloroform–hexane (1:3 by volume) gave an analytical sample, mp 148–149°.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.10; H, 7.46; N, 10.45. Found: C, 76.22; H, 7.31; N, 10.29.

A benzal derivative was prepared in the usual way. The crude product was recrystallized from hot ethanol to give an analytical sample, mp 177.5–179.5°.

Anal. Calcd for $C_{24}H_{24}N_2O$: C, 81.00; H, 6.75; N, 7.86. Found: C, 80.91; H, 6.84; N, 7.98.

The infrared spectrum of the product showed a medium absorption at 1625 cm^{-1} which can be assigned to C=N. The ultraviolet spectrum showed maxima at 250 mμ (ε 8300), 270 (4930), and 278 (4930), and a shoulder at 290 mμ (4500).

2,7-Diphenyl-4-hexahydroazepinone (8).—To a stirred suspension of 1 g of N-nitroso-2,7-diphenyl-4-hexahydroazepinone in 5 ml of glacial acetic acid was added dropwise a solution of 2 g of cuprous chloride in 6 ml of concentrated hydrochloric acid. Evolution of a gas which gave a positive starch–potassium iodide test proceeded readily and was complete after 1 hr. At this time, the reaction mixture was filtered and the solid was washed with successive portions of acetic acid. The dried solid was purified by thorough and vigorous mixing with dilute aqueous ammonium hydroxide. Filtration and air drying gave an off-white product which was further purified by repeated crystallization from hot hexane. The analytical sample melted at 110–111° and was obtained in 35% yield.

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.52; H, 7.16; N, 5.28. Found: C, 81.49; H, 7.10; N, 5.50.

Ethylene Thioketal of 2,7-Diphenyl-4-hexahydroazepinone (9).—To a suspension of 6 g of N-nitroso-2,7-diphenyl-4-hexahydroazepinone in 50 ml of gacial acetic acid was added, in succession, 6 ml of ethanedithiol and 12 ml of redistilled boron trifluoride etherate. The deep red solution was allowed to remain at room temperature for 24 hr, with occasional swirling. The precipitated solid was collected by filtration and washed thoroughly with ether. This solid (8 g, mp 260–262° dec), presumably a boron fluoride salt or addition compound, was converted into the free base by vigorous mixing with ether–concentrated ammonium hydroxide. The phases were separated and the ether layer was clarified by filtration and evaporated. The residue, an oil, readily crystallized on scratching. In this manner, 7 g (100%) of a solid with mp 64–81° was obtained. One recrystallization from hot ethanol gave an analytical sample, mp 89–90°.

Anal. Calcd for $C_{20}H_{23}NS_2$: C, 70.40; H, 6.75; N, 4.10; S, 18.75. Found: C, 70.46; H, 6.91; N, 3.99; S, 18.54.

2,7-Diphenylhexahydroazepine (10).—To a suspension of 3.4 g (0.01 mol) of the ethylene thioketal of 2,7-diphenyl-4-hexahydroazepinone in 200 ml of ethanol was added a slurry of 35 g of W-7 grade Raney nickel catalyst[10] in ethanol. The stirred mixture was heated at reflux for 20 hr. The hot mixture was filtered through a Celite mat. The filter cake was washed with several portions of hot solvent which were added to the filtrate. The solvent was removed under reduced pressure, leaving a yellow oil. The oil was dissolved in 5 ml of hot ethanol and, upon cooling slowly and scratching, crystallization was induced. After refrigeration, the air-dried solid had mp 88–94° and weighed 0.9 g (36%). Two recrystallizations from hot alcohol gave an analytical sample, mp 96–98°.

Anal. Calcd for $C_{18}H_{21}N$: C, 86.05; H, 8.36; N, 5.57. Found: C, 85.99; H, 8.31; N, 5.73.

It was found possible to prepare a picrate from ethanol–water. However, the derivative obtained, mp 175–180°, was not investigated further.

(9) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1948, p 171.

(10) H. R. Billica and H. Adkins in "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 179.

Wolff-Kishner Reduction of 2,7-Diphenyl-4-hexahydroazepinone.—A mixture of 2.2 g of **8** in 50 ml of diethylene glycol containing 2.5 g of potassium hydroxide and 2.5 ml of hydrazine hydrate was heated under reflux in an oil bath for 2 hr. The condenser was removed for a brief period to allow the more volatile components to boil away. Heating was continued at 190–210° for 3 hr. The cooled reaction mixture was poured over cracked ice and allowed to thaw. The clear supernatant layer was decanted from a yellow gum which had precipitated. The gum was taken up in 5 ml of hot ethanol which on cooling deposited 1.8 g (87%) of pale yellow solid, mp 100–108°. Several crystallizations from hot hexane and finally from acetic acid–water gave an analytical sample, mp 116–118°.

Anal. Calcd for $C_{18}H_{17}N$: C, 87.45; H, 6.85; N, 5.66; mol wt, 247. Found: C, 87.55; H, 6.95; N, 5.76; mol wt, 261.

The product gave an immediate, intense red coloration with 5% *p*-dimethylaminobenzaldehyde in concentrated hydrochloric acid, suggesting a pyrrole structure.[11] A mixture melting point with an authentic sample of 2-phenyl-5-(β-phenethyl)pyrrole (**12**) (see below) was not depressed and their infrared spectra were superimposable.

Methyl 4-Keto-6-phenyl Hexanoate (13).—The general procedure of Cason and Prout[12] was followed. A solution of phenylethylmagnesium bromide in 200 ml of anhydrous ether was prepared from 9.6 g (0.394 g-atom) of magnesium and 73 g (0.394 mol) of phenethyl bromide under a nitrogen atmosphere. To the stirred, ice-cold, Grignard solution was added 38.5 g (0.21 mol) of cadmium chloride during 5 min. The mixture was allowed to warm to room temperature, stirred for 1 hr at room temperature, and refluxed for 30 min. Most of the solvent was removed by distillation and replaced with dry benzene. A solution of 47.3 g (0.315 mol) of β-carbomethoxypropionyl chloride[13] in 100 ml of dry benzene was added with stirring during 1 hr. The mixture was heated under reflux for 2 hr and allowed to stir overnight at room temperature. Excess ice and dilute (3%) hydrochloric acid were added to the cooled reaction mixture. The details of further processing of the hydrolyzed mixture were as described. The oil remaining after removal of solvent was distilled under vacuum. The fraction with bp 120–123° (0.4 mm), $n^{26}D$ 1.5065, amounted to 35 g (51%).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.94; H, 7.27. Found: C, 70.95; H, 7.41.

δ-Benzyl Levulinic Acid (14).—A mixture of 22 g (0.1 mol) of methyl 4-keto-6-phenyl hexanoate and 30 g (1.3 mol) of sodium hydroxide in 500 ml of water was heated under reflux for 24 hr. The cooled reaction mixture was poured over 1 kg of cracked ice to which 100 ml of concentrated hydrochloric acid had been added. The white precipitate was collected, washed thoroughly with water, and air dried. The solid, 17.2 g (83.5%), had mp 90–92° (lit.[14] mp 89°).

1,6-Diphenyl-1,4-hexanedione (15).—To 17.2 g (0.08 mol) of δ-benzyllevulinic acid was added 10 ml of thionyl chloride. The mixture was kept at 50° (water bath) for 4 hr. Excess thionyl chloride was removed under the water-aspirator vacuum. To the residue was added 150 ml of dry benzene, followed by 22 g of aluminum chloride. The mixture was heated gently for 1 hr, cooled, and poured over cracked ice containing 100 ml of concentrated hydrochloric acid. The organic layer was separated, washed with 5% sodium carbonate solution and water, and dried. Removal of the solvent under reduced pressure left an orange oil. The oil was dissolved in 50 ml of hot ethanol, filtered, and cooled to give 4.5 g (21%) of tannish white crystals, mp 76–83°. Crystallization from methanol gave an analytical sample, mp 84–85°.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.76. Found: C, 81.37; H, 6.68.

The infrared spectrum exhibited twin carbonyl peaks at 1705 (CH_2COCH_2) and 1688 cm^{-1} (C_6H_5CO).

2-Phenyl-5-(β-phenethyl)pyrrole (12).—The general procedure of Kapf and Paal[15] for pyrrole ring closure was followed. A mixture of 0.3 g of 1,6-diphenyl-1,4-hexanedione, 0.8 g of ammonium acetate, and 10 ml of glacial acetic acid was heated under reflux for 1.5 hr. The dark purple solution was poured over cracked ice and the product was filtered. The off-white solid obtained was washed with water and air dried. Recrystallization from 5 ml of a 4:1 (by volume) mixture of acetic acid–water gave 0.1 g (40%) of pinkish crystals, mp 109–111°. Admixture with the product from the modified Wolff-Kishner reduction of 2,7-diphenyl-4-hexahydroazepinone gave mp 110–114°. The infrared spectra of the two material were superimposable.

Registry No.—**2**, 22187-77-5; **3**, 22187-78-6; **4**, 22187-79-7; 2,4-dinitrophenylhydrazone of **4**, 22212-31-3; **5**, 22187-80-0; **6**, 22188-04-1; **7**, 22187-81-1; benzal derivative of **7**, 22187-82-2; **8**, 22187-83-3; **9**, 22187-84-4; **10**, 22187-85-5; **12**, 22187-88-8; **13**, 22187-89-9; **15**, 1226-96-6.

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(11) I. F. Feigl, "Tupfelanalyse, Organische Teil," Akademische Verlagsgesellschaft H.B.H., Frankfurt Am Main, 1960, p 281.

(12) J. Cason and F. S. Prout, in ref 10, p 601.

(13) J. Cason, in ref 10, p 169.

(14) H. Staudinger and H. Schneider, *Ber.*, **56**, 699 (1923).

(15) S. Kapf and C. Paal, *ibid.*, **21**, 3053 (1888).