A Convenient Preparation of *trans*-β-Farnesene

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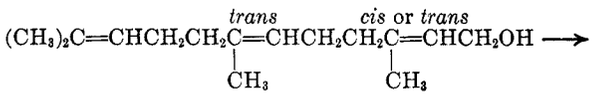
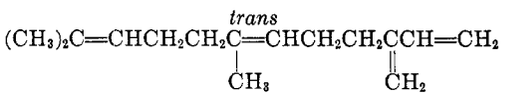
The dehydration of farnesol has been investigated by several workers, most recently by Naves,[1] who reported that the acid-catalyzed dehydration of farnesol yielded a complex mixture of at least 12 components. The base-catalyzed dehydration of farnesol to give *trans*-β-farnesene has also been reported.[2]



farnesol



trans-β-farnesene

In an effort to obtain larger amounts of pure *trans*-β-farnesene, we have repeated the base-catalyzed dehydration of farnesol. The reaction of farnesol with KOH at 200–210° leads to significant amounts of C_{14} olefins, which are difficult to separate by distillation. Consequently we examined a number of additional methods for dehydration, including the use of iodine, acid anhydrides, acid chlorides, $ZnCl_2$, and hot dimethyl sulfoxide. None of these methods proved satisfactory.

On the other hand, catalytic dehydration by means of activated alumina proved successful. The resulting *trans*-β-farnesene is obtained in 65% yield by passage over activated alumina at 260–270°.

The infrared spectrum of the product so obtained was identical with that of *trans*-β-farnesene isolated from the acid- or base-catalyzed dehydration of farnesol, as was the nmr spectrum.[2] Comparison was also made with a sample of natural *trans*-β-farnesene isolated from *Matricaria matricarioides*. Nerolidol may be similarly dehydrated in comparable yield. The application of this method to other sesquiterpene alcohols is being investigated.

Experimental Section

The dehydration was conducted in a Wilkens A-90 P gas chromatograph, using a 5 ft × 0.25 in. Pyrex column packed with glass beads (60–80 mesh) and 1.0 g of Alcoa F-20 chromatographic alumina. The alumina was activated by heating to 300°. The farnesol (Fluka AG) was injected in 100-μl portions, using a helium flow of 60 ml/min. From 5.0 g of farnesol, 4.26 g of crude product was obtained. The infrared spectrum showed that dehydration was complete at 260–270°. Glpc analysis of the product on a 10 ft × 0.25 in. 25% TCEP/60–80 Chrom W column at 130° showed a purity of 80% *trans*-β-farnesene: $n^{20}D$ 1.4887; $\lambda_{max}^{n\text{-heptane}}$ 224 mμ (ε 14,000); infrared spectrum (0.025-mm cell), 3095 (m), 2970 (s), 2930 (s), 2730 (w), 1790–1820 (w), 1670 (w), 1645 (w), 1630 (w), 1592 (s), *ca.* 1440 (s), 1378 (sh), 1372 (s), 1150 (w), 1105 (m), 990 (s), 900 (sh), 890 (s), 825–835 (m), 740–755 (w), and *ca.* 670 (w).

(1) Y. Naves, *Helv. Chim. Acta*, **49**, 1029 (1966).
(2) A. Bhati, *Perfumery Essent. Oil Record*, **53**, 376 (1962).

Registry No.—*trans*-β-Farnesene, 502-60-3.

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1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine

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The synthesis[1] and pharmacological activity[2] of 1-(*p*-chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (VII) was reported previously from this laboratory. The reaction of 2-(*p*-chlorobenzoyl)benzoic acid with ethylenediamine afforded the tricyclic intermediate (VIII), which upon reaction with lithium aluminum hydride yielded VII. The structural assignment was based on elemental analyses and infrared and nmr spectral data of VII and derivatives. Although a careful examination of these data left little doubt as to the validity of the assigned structure, nonetheless a chemical proof of the structure of VII was desired. This paper describes an unequivocal synthesis of VII. See (Chart I).

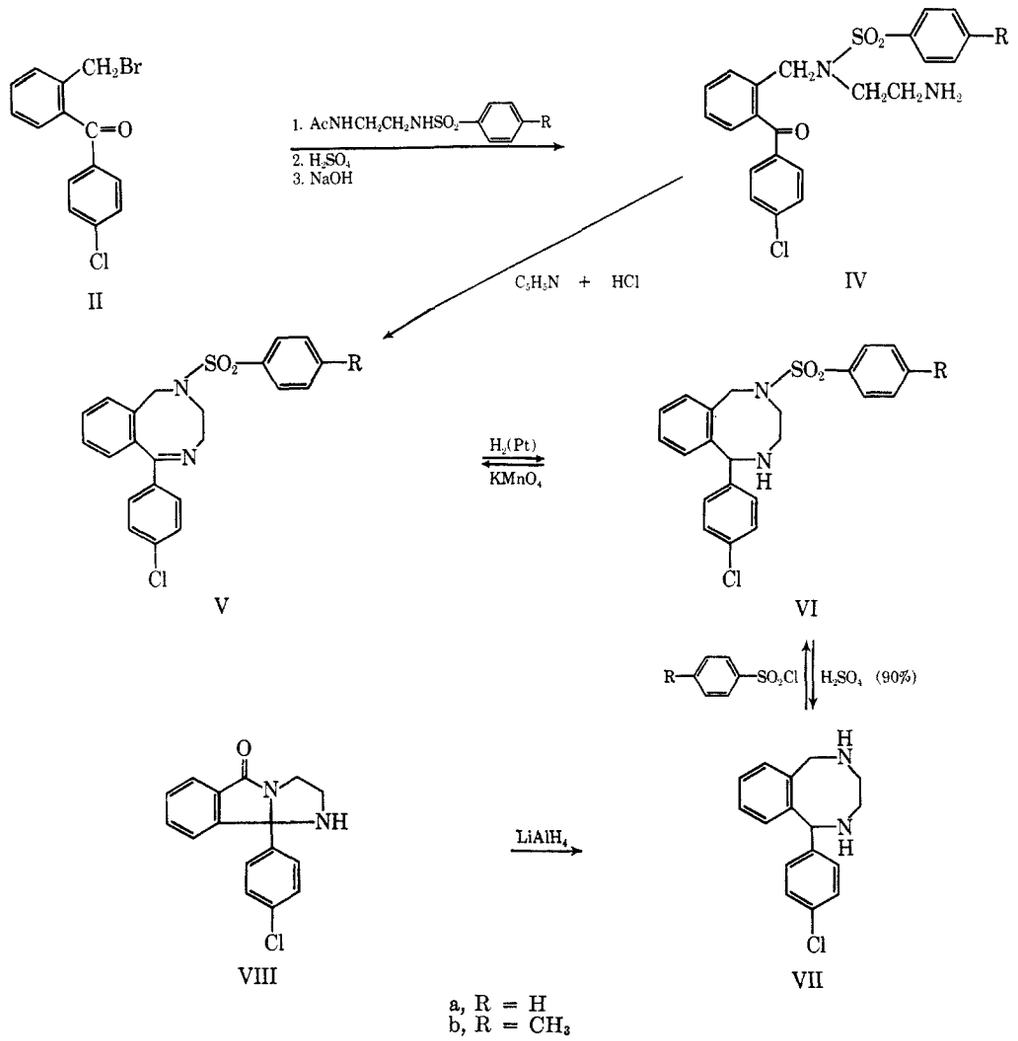
Bromination of 4-chloro-2′-methylbenzophenone (I) with N-bromosuccinimide in carbon tetrachloride afforded 2′-bromomethyl-4-chlorobenzophenone (II) as starting material in the synthesis. The reaction of II with N-acetyl-N′-phenylsulfonylethylenediamine in refluxing ethanol containing an equivalent amount of potassium hydroxide gave N-acetyl-N′-(2-*p*-chlorobenzoylbenzyl)-N′-phenylsulfonylethylenediamine (IIIa). Hydrolysis of IIIa with 20% sulfuric acid afforded the amine IVa. Several attempts to cyclize IVa to 1-(*p*-chlorophenyl)-5-phenylsulfonyl-3,4,5,6-tetrahydro-2,5-benzodiazocine (Va) by heating with azeotropic removal of water were unsuccessful. The cyclodehydration was effected by refluxing IVa in pyridine containing a catalytic amount of pyridine hydrochloride. The presence of a small amount of an acid appears to be essential for the ring closure to occur. In the absence of the catalyst only starting material was recovered after 2 days of refluxing.

The formation of Va was accompanied by distinct infrared spectral changes. The amino N–H stretching band (3390 cm^{-1}) and carbonyl absorption peak (1660 cm^{-1}) of N-(2-*p*-chlorobenzoylbenzyl)-N-phenylsulfonylethylenediamine (IVa) were absent in the benzodiazocine Va. The appearance of a new band at 1620 cm^{-1} indicated the development of a >C=N bond.

1-(*p*-Chlorophenyl)-3,4,5,6-tetrahydro-5-(*p*-tolylsulfonyl)-2,5-benzodiazocine (Vb) was prepared by the same reaction sequence used for the synthesis of Va.

(1) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).
(2) (a) M. I. Gluckman, *Pharmacologist*, **7** (2), 146 (1965); (b) T. Baum, *ibid.*, **7** (2), 147 (1965); (c) R. J. Bower and J. B. Kobb, *ibid.*, **7** (2), 147 (1965).

CHART I



The crude product from the reaction of II with N-acetyl-N′-(*p*-tolylsulfonyl)ethylenediamine was hydrolyzed directly to give N-(2-*p*-chlorobenzoylbenzyl)-N-(*p*-tolylsulfonyl)ethylenediamine (IVb), which was similarly cyclized to yield Vb.

Catalytic hydrogenation of Va and Vb with a theoretical amount of hydrogen afforded VIa and VIb respectively, with a resultant loss of the 1620-cm^{-1} band in their spectra. Oxidation of VIb with potassium permanganate in acetic acid regenerated Vb with selective oxidation of the C_1–N_2 bond. The nmr spectrum of VIa revealed the presence of a singlet at δ 5.30 for the methinyl proton. The amino proton was observed as a broad singlet at δ 1.72 which vanished upon deuteration. Four protons of the methylene groups bridging the two nitrogen atoms appeared as an AA′BB′ pattern centered at δ 3.17. The benzylic protons appeared as a doublet at δ 5.32 and 4.58 (J = 14 cps), indicating their magnetic nonequivalency. In the case of Va both of the benzylic protons were shifted upfield, with one proton exhibiting an especially large change [δ 4.93, 3.22 (J = 14 cps)]. The diamagnetic shift may possibly be due to a shielding effect of the C=N bond.[3] A molecular model of Va shows that one of the benzylic protons lies within the shielding cone of the >C=N. In contrast, the benzylic protons of the open-chain compound IVa appeared as a singlet at δ 4.48.

Treatment of VIa or VIb with 90% sulfuric acid afforded VII, which was isolated as a dihydrochloride salt. The material obtained by this procedure was identical with VII prepared by the earlier method.[1] When VII was allowed to react with benzenesulfonyl chloride in aqueous alkaline medium at room temperature, VIa was formed in excellent yield, indicating that no basic structural change had occurred during the hydrolysis.

(3) A typical example of magnetic shielding by a C=C was reported by W. L. Meyer and R. W. Huffman, *Tetrahedron Letters*, No. 16, 691 (1962).

Experimental Section

The melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer Model 21 spectrophotometer, and nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer using tetramethylsilane as internal standard.

4-Chloro-2′-methylbenzophenone (I) was prepared by the reported method.[4] The product, bp 108–109° (0.1 mm), lit.[4] bp 194° (14 mm), was homogeneous on thin layer chromatographic plates and its nmr spectrum (A_2X_2 quartet centered at δ 7.59, 4 H, *p*-disubstituted benzene) indicated that no 2-chloro-2′-methylbenzophenone was present. **N-Acetyl-N′-phenylsulfonylethylenediamine** and **N-acetyl-N′-(*p*-tolylsulfonyl)ethylenedi-**

(4) H. de Diesbach and P. Dobbelmann, *Helv. Chim. Acta*, **14**, 369 (1931).

amine were prepared by the method reported by Amundsen and Longley.[5]

2'-Bromomethyl-4-chlorobenzophenone (II).—A well-blended mixture of 5.9 g of N-bromosuccinimide and 0.1 g of benzoyl peroxide was added to 100 ml of a warm, dry carbon tetrachloride solution containing 11.5 g of 4-chloro-2'-methylbenzophenone. The resulting mixture was heated to reflux, with occasional shaking, for 45 min. Succinimide was removed by filtration of the hot solution. The filtrate was concentrated under reduced pressure to give a green oil which crystallized on scratching. Recrystallization from petroleum ether (bp 60–90°) using charcoal afforded 4.1 g of product with mp 84–87°, infrared absorption (KBr) at 1653 cm^{-1} (C=O), and nmr signals at δ 4.70 (2 H singlet) and at 7.55 (centered, 8 H aromatic multiplet). This compound decomposed slowly on standing, and was kept under refrigeration.

Anal. Calcd for $C_{14}H_{10}BrClO$: C, 54.31; H, 3.26; Br, 25.81; Cl, 11.45. Found: C, 54.42; H, 3.15; Br, 25.35; Cl, 11.2.

N-Acetyl-N'-(2-*p*-chlorobenzoylbenzyl)-N'-phenylsulfonylethylenediamine (IIIa).—To a solution of 15 g of II and 4.7 g of potassium hydroxide (85%) in 70 ml of absolute alcohol was added 17 g of N-acetyl-N'-phenylsulfonylethylenediamine, in small portions and with mechanical stirring. The resulting mixture was heated to reflux for 30 min and allowed to cool to room temperature. The precipitated salt was removed by filtration. The filtrate was concentrated under reduced pressure and treated with 100 ml of 2 *N* sodium hydroxide solution. The product was extracted with ether. Addition of 150 ml of water to the ether solution caused separation of a precipitate, which was collected on a filter and washed with ether several times to give 16 g of white crystals, mp 103–105°. Recrystallization from carbon tetrachloride and heptane gave an analytical sample with mp 103.5–105° and infrared absorption (KBr) at 3268 (NH), 1667 (shoulder, C=O), and 1657 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{23}ClN_2O_4S$: C, 61.20; H, 4.92; Cl, 7.54; N, 5.95; S, 6.81. Found: C, 60.84; H, 4.74; Cl, 7.5; N, 6.15; S, 6.7.

N-Acetyl-N'-(2-*p*-chlorobenzoylbenzyl)-N'-(*p*-tolylsulfonyl)ethylenediamine (IIIb) was prepared in the same way as IIIa from 7.7 g of 2'-bromomethyl-4-chlorobenzophenone, 7.7 g of N-acetyl-N'-(*p*-tolylsulfonyl)ethylenediamine, 2.0 g of potassium hydroxide (85%), and 30 ml of absolute ethanol. The product separated as an oil which failed to crystallize and which was used directly in the following reaction.

N-(2-*p*-Chlorobenzoylbenzyl)-N-phenylsulfonylethylenediamine (IVa).—A mixture of 2.5 g of IIIa and 25 ml of 20% (v/v) sulfuric acid was heated under reflux for 4 hr and allowed to stand overnight at room temperature. The solid cake which separated was washed with water and with ether and was filtered under suction to give 1.8 g of crude product. Three recrystallizations from water afforded an analytical sample with mp 126–128° and infrared absorption (KBr) at 2857 ($NH_3^{\oplus}$) and 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{22}ClN_2O_3S \cdot {}^1/_2SO_4$: C, 55.29; H, 4.64; Cl, 7.42; N, 5.86; S, 10.05. Found: C, 55.33; H, 4.66; Cl, 7.4; N, 5.72; S, 10.0.

N-(2-*p*-Chlorobenzoylbenzyl)-N-(*p*-tolylsulfonyl)ethylenediamine (IVb) was obtained in the same way by hydrolyzing IIIb. Recrystallization from water afforded needles with mp 165–167° and infrared absorption (KBr) at 2857 ($NH_3^{\oplus}$) and 1661 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{24}ClN_2O_3S \cdot {}^1/_2SO_4$: C, 56.14; H, 4.92; Cl, 7.21; N, 5.70; S, 9.78. Found: C, 56.09; H, 4.61; Cl, 7.5; N, 5.70; S, 9.9.

1-(*p*-Chlorophenyl)-5-phenylsulfonyl-3,4,5,6-tetrahydro-2,5-benzodiazocine (Va).—The sulfate of IVa was converted to a free amine by treatment with 30% sodium hydroxide solution on a steam bath for 15 min. A solution obtained by dissolving 15.0 g of the crude, dried free amine and 5.4 g of dry pyridine hydrochloride in 600 ml of pyridine was refluxed for 20 hr. The pyridine was removed by evaporation under reduced pressure and the product was extracted into ether. The ether extract was washed three times with water and dried over magnesium sulfate. Evaporation of the solvent afforded an oil which upon treatment with 95% ethanol yielded 7.6 g of solid. Recrystallization from dilute ethanol gave an analytical sample with a melting point of 115–117° and infrared absorption (KBr) at 1620 cm^{-1} (C=N).

Anal. Calcd for $C_{22}H_{19}ClN_2O_2S$: C, 64.30; H, 4.66; Cl, 8.63; N, 6.82; S, 7.80. Found: C, 64.16; H, 4.40; Cl, 8.40; N, 6.57; S, 7.8.

1-(*p*-Chlorophenyl)-3,4,5,6-tetrahydro-5-(*p*-tolylsulfonyl)-2,5-benzodiazocine (Vb) was prepared, similarly to Va, from 1.4 g of IVb·sulfate, affording 0.85 g of product with mp 173–174.5° (from alcohol), infrared absorption (KBr) at 1620 cm^{-1} (C=N), and nmr signals at δ 2.40 (3 H singlet, $-CH_3$), at 3.25, 4.07 (4 H crude triplet, $-CH_2CH_2-$), at 3.20, 4.93 (2 H doublet, CH_2 at C_6), and at 7.0–8.0 (12 H aromatic multiplet).

Anal. Calcd for $C_{23}H_{21}ClN_2O_2S$: C, 65.01; H, 4.98; Cl, 8.34; N, 6.59; S, 7.55. Found: C, 64.85; H, 4.79; Cl, 8.4; N, 6.76; S, 7.5.

From VIb.—A potassium permanganate solution (0.8 g/50 ml of water) was added dropwise, with stirring, to a solution obtained by dissolving 2.1 g of VIb in 30 ml of glacial acetic acid at room temperature over a period of 2.5 hr. The resulting mixture was stirred for an additional 0.5 hr and filtered. The filtrate was treated with charcoal and refiltered. Removal of acetic acid under reduced pressure and recrystallization of the residue from absolute ethanol afforded 0.3 g of product, identical with the product obtained from IVb.

1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-5-phenylsulfonyl-2,5-benzodiazocine (VIa). From Va.—A solution of 0.38 g of Va in 20 ml of methanol containing 0.07 g of PtO_2 was allowed to absorb the theoretical amount of hydrogen under atmospheric pressure. The methanol was removed to afford 0.35 g of crude product. Recrystallization from ethanol and water gave material with mp 147–146° and infrared absorption (KBr) at 3333 cm^{-1} (NH), no absorption peak in C=O and C=N region.

Anal. Calcd for $C_{22}H_{21}ClN_2O_2S$: C, 63.99; H, 5.13; Cl, 8.59; N, 6.77; S, 7.77. Found: C, 63.65; H, 5.02; Cl, 8.6; N, 6.78; S, 8.0.

From VII.—Benzenesulfonyl chloride (1.8 g) was added to a mixture of 3.46 g of VII·2HCl and 2.94 g of sodium bicarbonate in 50 ml of water and the resulting mixture was stirred vigorously for 0.5 hr. The solid which formed was separated by filtration and washed with water several times. Recrystallization from ethanol afforded 3.18 g of product with mp 148–150° and infrared spectrum identical with that of benzodiazocine VIa prepared from Va.

1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-5-(*p*-tolylsulfonyl)-2,5-benzodiazocine (VIb). From Vb.—Catalytic hydrogenation of Vb (0.43 g) in ethanol with a theoretical amount of hydrogen using 0.07 g of PtO_2 afforded 0.43 g of VIb with mp 135–137°, infrared absorption (KBr) at 3300 cm^{-1} (NH), and nmr signals at δ 2.42 (3 H singlet), at 3.16 (4 H multiplet, $-CH_2CH_2-$), at 4.57, 5.29 (two doublets, J = 14 cps) (2 H, CH_2 at C_6), at 6.8–78 (12 H aromatic multiplet), and at 1.63 (1 H singlet, NH), the latter disappearing upon deuteration.

Anal. Calcd for $C_{23}H_{23}ClN_2O_2S$: C, 64.70; H, 5.43; Cl, 8.31; N, 6.56; S, 7.51. Found: C, 64.88; H, 5.39; Cl, 8.35; N, 6.63; S, 7.5.

From VII.—Compound VIb (10.1 g) was obtained from 17.3 g of VII·2HCl following the procedure used for VIa.

1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (VII).—A mixture of 0.7 g of VIa and 10 ml of 90% (v/v) sulfuric acid was heated in a steam bath for 2 hr and kept at room temperature for 1 hr. The solution was quenched with 20 g of crushed ice and adjusted with 40% sodium hydroxide solution to pH ~ 9. It was extracted four times with ether and the extract was washed with water and dried ($MgSO_4$). Removal of the ether afforded the product as an oil. The hydrochloride salt of VII was prepared by dissolving the oil in 10 ml of absolute ethanol and saturating the solution with anhydrous HCl gas. The precipitate thus obtained amounted to 0.3 g, mp 318° dec. A mixture melting point with VII·2HCl prepared alternatively as previously described[1] gave no depression. The infrared and nmr spectra of both samles were identical.

In the same manner, 0.6 g of VIb afforded 0.4 g of VII·2HCl.

Registry No.—II, 13958-71-9; IIIa, 13958-72-0; IVa, 13958-73-1; IVb, 13958-74-2; Va, 13958-75-3; Vb, 13958-76-4; VIa, 13958-77-5; VIb, 13958-78-6; VII, 13958-79-7.

(5) L. H. Amundsen and R. I. Longley, Jr., *J. Am. Chem. Soc.*, **62**, 2811 (1940).

Acknowledgment.—The authors are grateful to Dr. G. Ellis and his staff for the microanalyses, Dr. C. Hetzel for the nmr spectra, Mr. B. Hofmann for the infrared spectra, and Mr. L. E. McCardle for technical assistance.

The Conversion of Steroidal α-Bromo Ketones into Ketols by Means of Hydrazine[1]

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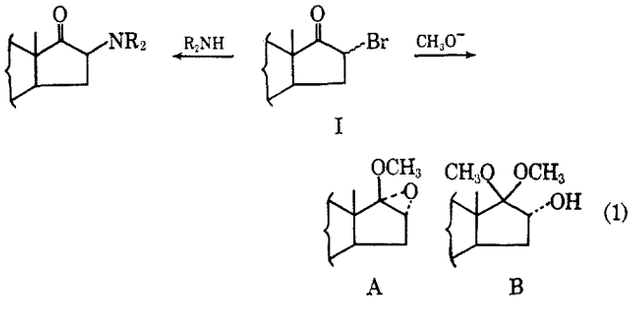
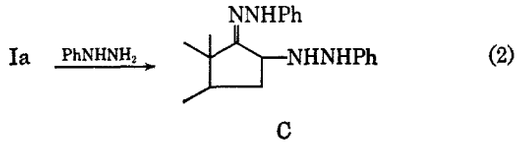
Recent studies on the chemistry of 16-bromo-17-keto steroids (I)[2] indicated that direct displacement of bromide by amines is possible in these α-bromo ketones. On the other hand, methoxide ions attacked at the carbonyl function with formation of ketal (B) *via* epoxide intermediates (A)[3] (eq 1).

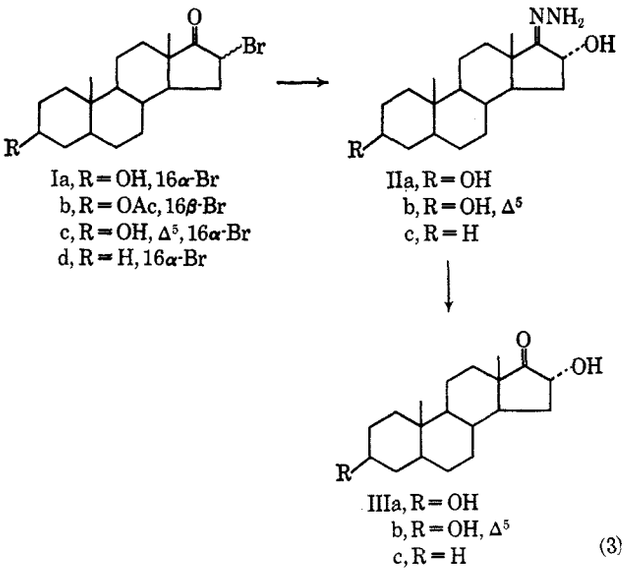


(1)

In conjunction with our investigation of the mechanism of osazone formation in the reaction of α-substituted ketones with phenylhydrazine,[4] we explored the reaction of steroidal α-bromo ketones with hydrazine itself. In contrast to the conversion of Ia into C with phenylhydrazine (eq 2)[4] treatment of 16α-bromoandrostan-3β-ol-17-one (Ia) with an excess of hydrazine hydrate in ethanol leads in 90% yield to 3β,16α-dihydroxyandrostan-17-one hydrazone (IIa). The structure of the latter was apparent from elemental analysis, infrared spectrum (ν_{max} 3400–3250 cm^{-1} (OH and NH), 1670 cm^{-1} (C=N)), and acid hydrolysis to the 17-keto-16α-ol (IIIa) (eq 3).

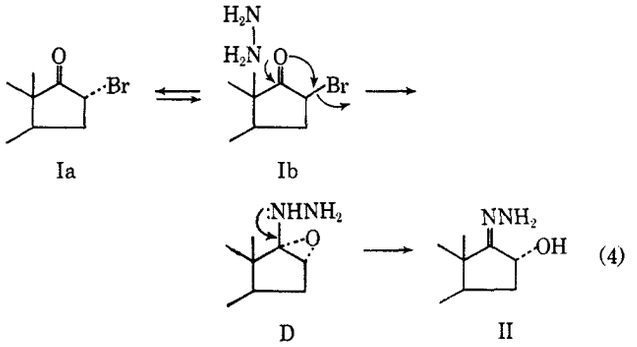


(2)

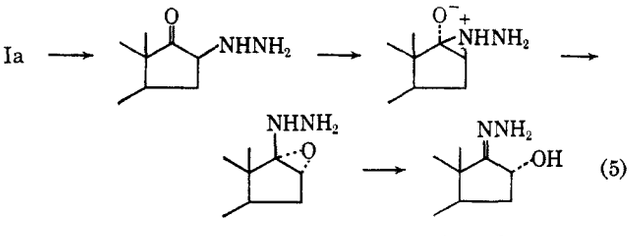


(3)

Ketols of type III are known to be stable under acid conditions although they are easily isomerized in basic medium.[3,5] Reduction of IIIa or IIIc with lithium aluminum hydride leads to 16α,17β-diols. Since the formation of II from I occurs with aqueous or anhydrous hydrazine, it can best be rationalized as in eq 4. This is analogous to the reaction of sodium methoxide with I which presumably proceeds through a similar epoxide intermediate (A). The 16α configuration of hydroxyl in II and III requires an α-epoxide intermediate (D) and hence the reaction should proceed *via* 16β-bromo 17-ketone (Ib). In fact, the 16β-bromo steroid Ib likewise gives II upon exposure to hydrazine. Another plausible mechanism consistent with our data has been suggested by the referee (eq 5).



(4)



(5)

The reaction of bromo ketones Ia or b with hydrazine constitutes a useful synthesis of 16α-hydroxy-17-ketoandrostanes and hence of 16α,17β-diols. In the same manner Ic and d were converted into IIIb and c, respectively.

(1) Stereochemistry. XXVI. For paper XXV, see A. Hassner and F. W. Fowler, *Tetrahedron Letters*, 1545 (1967).

(2) (a) C. L. Hewett and D. S. Savage, *J. Chem. Soc.*, 484 (1966); (b) A. Hassner and P. Catsoulacos, *J. Org. Chem.*, **32**, 549 (1967).

(3) A. Hassner and P. Catsoulacos, *ibid.*, **31**, 3149 (1966).

(4) A. Hassner and P. Catsoulacos, *Tetrahedron Letters*, 489 (1967); *Chem. Commun.*, 121 (1967).

(5) N. L. Leeds, O. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).