9,3-Oxazatricyclo[3.3.1.$0^{2,4}$]nonan-7-one, a Novel Hetero-tricyclic Ring System Produced by Bicyclizative Condensation of Acetone with *cis*-2,3-Dibenzoylaziridines (1)

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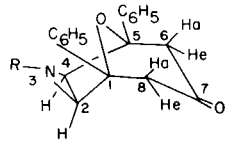
Sir:

During the study of the significant solvent dependency of the *cis-trans* equilibrium position of 1-benzyl-2,3-dibenzoylaziridine **4a** ⇌ **5a** in base catalyzed epimerization (2), a new compound crystallized in 43% yield upon cooling the refluxing 0.17 *M* sodium 2-propoxide solution, which is now shown by analyses and spectral data to be 3-benzyl-1,5-diphenyl-9,3-oxazatricyclo[3.3.1.$0^{2,4}$]nonan-7-one (**1a**). This compound is the result of equimolar bicyclizative condensation of *cis*-dibenzoylaziridine (**4a**) with acetone produced by oxidation of 2-propoxide in concomitant reduction of one of the carbonyl groups of **4a** or **5a** in the equilibrating mixture, and it is obtained as the exclusive product of the condensation of directly added acetone with either **4a** or **5a** in ethanolic sodium ethoxide. This novel hetero-tricyclic ketone is of particular interest because of its skeletal relationship to the physiologically active scopine **2** with the ring oxygen and nitrogen atoms interchanged. Presumably the conformation of the tetrahydro-4-pyrone ring of **1** corresponds to the chair conformation of the piperidone ring of tropinone **3** (3), and the skeletal configuration of **1** corresponds to that of scopine **2** (4).



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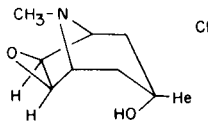

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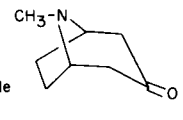

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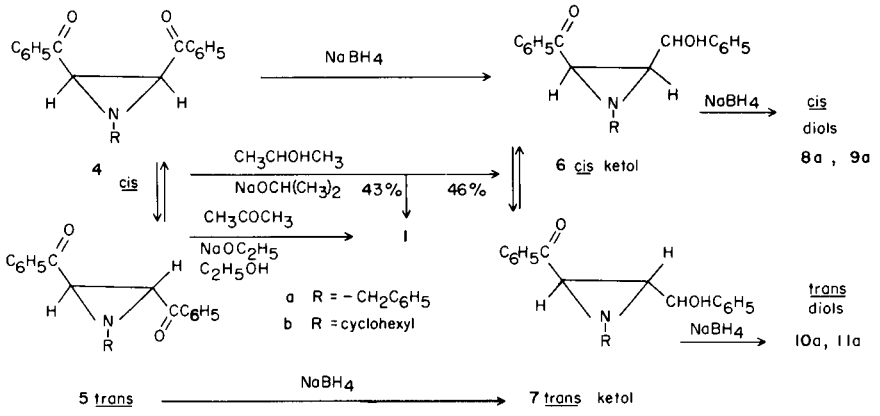
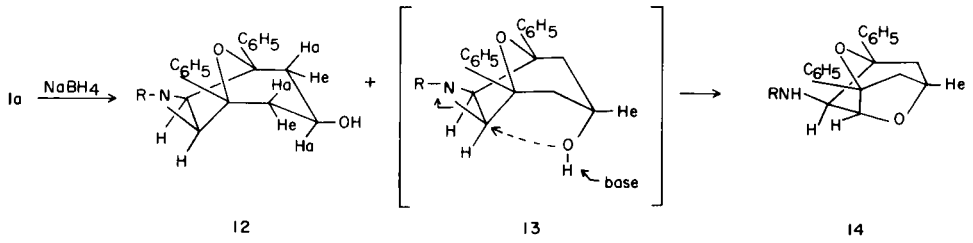
The product of the above reduction by which the acetone was generated, precipitated in 46% yield upon hydrolytic quenching of the filtrate of the 2-propoxide solution. Nmr analysis (2) showed it to be an equilibrium mixture, 1:1, of *cis* and *trans*-1-benzyl-2-benzoyl-3-(phenylhydroxymethyl)aziridines, the ketols **6a** and **7a** respectively.

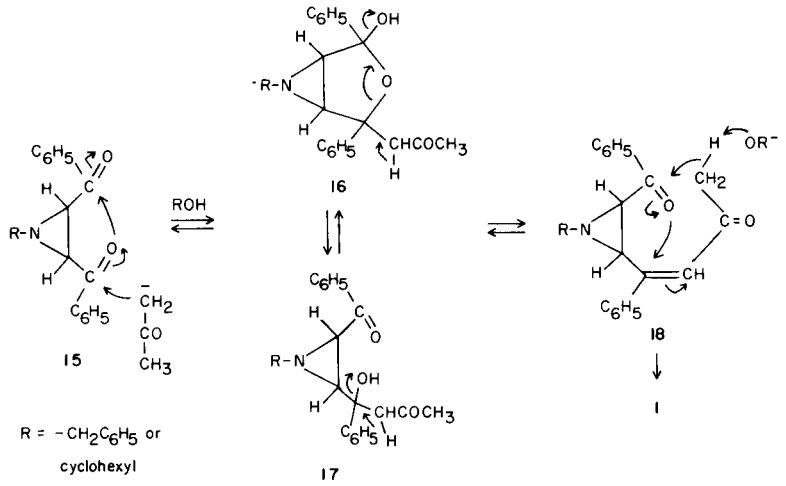
Reduction of *cis*-dibenzoylaziridine (**4a**) in ethanol with sodium borohydride (5) [0.25 mole per mole of substrate (mpms)] have only one of the two possible diastereoisomeric *cis* ketols, **6a**. Similar sodium borohydride reduction of the *trans* isomer **5a** afforded also only one of the two possible diastereoisomeric *trans* ketols **7a**. These ketols were further reduced by 0.25 mpms sodium borohydride solutions to the corresponding *cis*- and *trans*-1-benzyl-2,3-di(phenylhydroxymethyl)aziridine diastereoisomeric pairs, the diols **8a**, **9a**, and **10a**, **11a** respectively, each pair of which was separated chromatographically. The same two pairs of compounds were obtained by reduction of **4a** and **5a**, respectively, with 0.50 mpms sodium borohydride. The reduction exclusively of one carbonyl group first, rather than the formation of a statistical mixture of reduction products, is consistent with the activation of that carbonyl group by the other carbonyl group conjugated with it through the aziridine ring and with loss of that activation after reduction of the first carbonyl group.

The sodium borohydride reduction of **1a** produced two isomers (98%) which were separated chromatographically, [12]/[14] = 73/27. Compound **12**, an alcohol whose nmr spectrum possesses the unique A_2B_2X pattern (6), has been assigned the conformation with equatorial-OH. Compound **14**, not an alcohol, was the result of isomerization of the unisolated epimeric alcohol **13** (axial-OH) and arises by transannular attack of the 7-oxy anion at C-2 or C-4 with aziridine ring opening and Walden inversion, a process analogous to the formation of scopoline from scopine (4). This isomerization to **14** supports the assigned conformations and configurations of the tricyclic compounds. Since compound **14** is formed exclusively from **12** under conditions which would be expected to equilibrate **12** and **13** (7), and since **12** does not isomerize to **14** under the sodium borohydride reduction conditions, the above ratio of reduction products (73:27) closely represents the kinetic control of the formation of **12** and **13** under these conditions.

The formation of **1** may be rationalized in terms of two successive aldol condensations (**15**, **18**) between the acetone methyl groups each with one of the two *cis*-dibenzoylaziridine carbonyl groups, and loss of one







molecule of water (**16-17**), to give an α,β-unsaturated ketone **18**. The remarkably stable hetero-tricyclic ketone ring system of **1** is then consummated by the difficultly reversible oxygen bridging step which involves an intramolecular Michael reaction of the α,β-unsaturated ketone system in **18**. Important factors facilitating the bicyclizative condensation presumably are activation of a carbonyl group by the α-nitrogen and by the other carbonyl group conjugated with it through the aziridine ring, and *cis* group proximity effects which become enhanced by steric buttressing of the entering acetone methylene groups.

The bicyclizative condensation bears analogy to the Robinson-Schöpf synthesis of tropinone **3** from succinic dialdehyde, methylamine, and acetone or its derivatives (8). In a preliminary attempt to prepare 9-aza analogs of **1**, the condensation of acetone and *cis*-dibenzoylaziridine (**4a**) was performed in ammonia-saturated ethanolic sodium ethoxide; only **1a** was obtained.

Either *cis*- or *trans*-1-cyclohexyl-2,3-dibenzoylaziridine, **4b** or **5b**, reacts with acetone in sodium ethoxide solution to give **1b**. Use of sodium 2-propoxide solution gave, in addition to **1b**, an equilibrium mixture of ketols **6b** and **7b**.

When either **4a** or **5a** was treated with ethanolic sodium ethoxide containing butanone, the 6-methyl analog **19** of **1a** resulted; however, 3-pentanone failed to react when treated similarly. Presumably the initial *intermolecular* base-catalyzed aldol condensation step requires one unsubstituted acetone methyl group; whereas, the subsequent *intramolecular* aldol condensation step is not subject to steric hindrance by an α-substituted acetone methyl group.

Investigations are continuing on the mechanism and on effects of various substituents. We are extending the reaction to symmetrically and unsymmetrically substituted alkane, alkene, cyclopropane, oxirane, and other aziridine dicarbonyl derivatives, especially toward syntheses of compounds more closely analogous to the tropane alkaloid type drugs.

Data (9). **1a**: m.p. 143-144°; uv max (100% ethanol) 252 (ϵ, 520), 258 (ϵ, 630), 264 mμ (ϵ, 490); ir (potassium bromide), 1710 cm^{-1}; nmr (deuteriochloroform), δ 2.532 (s, 2), 3.372 (s, 2), 7.0 (m, 5), 7.4 (m, 10), AB quartet ν_B 2.805, ν_A 2.763 ppm (4, J = | 17.0 | Hz); nmr (C_6H_6) δ 1.908 (s, 2), 2.859 (s, 2), AB quartet ν_B 2.451, ν_A 2.635 ppm (4, J = | 17.0 | Hz).

1b: m.p. 123.5-125°. **6a**: m.p. 144.5-146°. **6b**: m.p. 165-166°. **7a**; m.p. 129-130.5°. **7b**: m.p. 134-135°. **8a**: m.p. 87-88°. **9a**: m.p. 116-118°. **10a**: m.p. 133.5-135°. **11a**: m.p. 126-128°.

12a: m.p. 180.5-182°: nmr (deuteriochloroform), A_2B_2X pattern of two quartets ν_B 1.712, ν_A 2.407 and a triplet of triplets ν_X 4.444 ppm (J_{AB} = | 13.0 |, J_{AX} = | 6.4 |, J_{BX} = | 10.4 | Hz).

14a: m.p. 101.5-103°. **19**: m.p. 170.5-172°.

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(9) New compounds gave satisfactory carbon and hydrogen analyses. Nmr recorded at 100 Mc in the solvent indicated; δ values are reported in ppm, ± 0.002 ppm, and J values in Hz, ± 0.2 Hz.

Received April 26, 1968 Charlottesville, Va. 22901