TABLE II
INFRARED ABSORPTION MAXIMA OF
HYDROXYBENZOPHENONES (CM^{-1})

Compound	$\nu_{C=O}$ (CCl_4)	$\nu_{C=O}$ (DMSO)
Benzophenone	1664[a]	1657[a b]
p-Hydroxybenzophenone	1661[c]	1645[d]
o-Hydroxybenzophenone	1633[a]	1659[d] 1626[e]
2,4-Dihydroxybenzophenone	1632[c]	1624[d] ~1620-1600[e]

[a] Concentration 2% (w/v). [b] The difference in $\nu_{C=O}$ in CCl_4 and DMSO is comparable to those found with other carbonyl compounds; *cf.* C. D. Ritchie, B. A. Bierl, and R. J. Honour, *J. Am. Chem. Soc.*, **84,** 4687 (1962). [c] Concentration 0.1%. [d] Concentration 5%. [e] Weaker of two bands observed.

ably due to an intermolecularly hydrogen-bonded species involving the phenol and a solvent molecule.[25] The 2,4-dihydroxy derivative does not show a non-hydrogen-bonded carbonyl absorption. This observation is in agreement with the finding that the *ortho* ct transition of this compound in DMSO is not shifted to higher energy (Table I) as is the case for the *o*-hydroxy compound. The reason the 2,4-dihydroxy compound does not form an intermolecular hydrogen bond is probably due to the electron-donating effect of the *p*-hydroxy group. This electron donation would increase the electron density on the carbonyl oxygen atom compared with the *o*-hydroxy compound and therefore strengthen the intramolecular hydrogen bond.[27]

In the nonhydroxylic solvents the small red shifts expected for the $\pi \rightarrow \pi^*$ transitions of *o*-hydroxybenzophenone and the 2,4-dihydroxy derivative are observed. The hydroxylic solvents produce the opposite effect. Some other subtle factors must be in effect in this case.[28] Perhaps the phenolic hydroxyl groups are also involved more directly in these $\pi \rightarrow \pi^*$ transitions than is apparent from the simplified theory presented in this paper.

Acknowledgment.—The author wishes to thank Dr. J. C. Evans for many helpful discussions during this work. Thanks are also due to Dr. J. C. Gavan for obtaining the infrared data, to Mr. J. Simek for checking some of the ultraviolet data, and to Mrs. W. L. Dilling for the mass spectral analyses.

[25] Other cases of effective hydrogen bonding between phenols and DMSO have recently been reported.[26]

[26] (a) G. J. Karabatsos and F. M. Vane, *J. Am. Chem. Soc.*, **85,** 3886 (1963); (b) R. J. Ouellette, *Can. J. Chem.*, **43,** 707 (1965).

[27] See Z. Yoshida and M. Haruta, *Tetrahedron Letters*, 3745 (1965). The author wishes to thank a referee for bringing this reference to his attention.

[28] Blue shifts are known for $\pi \rightarrow \pi^*$ transitions.[2a]

Dimeric Dihydroresorcinol.
6-(3-Ketocyclohexenyl)-5-ketohexanoic Acid[1]

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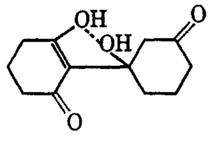
Received November 23, 1965

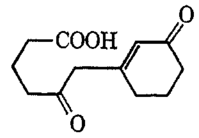
Evidence which requires the reformulation of the dimer of 1,3-cyclohexanedione as 6-(3-ketocyclohexenyl)-5-ketohexanoic acid includes λ_{max}^{EtOH} 238 mμ (log ϵ 4.14), indicative of a conjugated enone system, a solution in aqueous bicarbonate without change in absorption spectrum, a formation of the enolate (pK_a = 10.8) of the enedione system with $\lambda_{max}^{2N NaOH}$ 397 mμ (*ca.* 4.7), and the formation of a *p*-bromophenacyl ester. Dehydration of the dimer gives 2-(3-ketocyclohexenyl)cyclohexane-1,3-dione, predominately in the enol form, in which the two chromophoric systems are independent of one another due to the noncoplanarity of the ring systems. The difference in the acidity of the dehydrated dimer and the hydrogenated dehydrated dimer is an approximate measure of the difference in acid-strengthening effect of an sp^2 carbon as compared to an sp^3 carbon and amounts to 3.9 p*K* units.

We prepared a sample of Stetter's dimeric dihydroresorcinol[2] in the hope that it could be caused to condense further to a bridged polycyclic system in the manner that may account for the products arising from the acid hydrolysis of 2,2′,4,4′,6,6′-hexamethyl-4,4′-bi-4H-pyran.[3] In the course of working with this substance we were led to inquire into the accuracy of the original structural assignment. Stetter's formulation of the dimerization of cyclohexane-1,3-dione and the subsequent structure proof by dehydration, catalytic reduction, and retro-Claisen—Wolff–Kishner reduction to the known 6-cyclohexylhexanoic acid proceeded as in Scheme I.

Subsequently, Eskola[4] prepared the same dimer under different conditions and reported its ultraviolet spectrum to exhibit a maximum at 239 mμ in ethanol. While **2** might conceivably give an ultraviolet absorption if it existed in an enol form **6**, and the stability of the enolic form of the dimer due to internal hydrogen bonding might explain the unusually high conversion of a ketone to its aldol condensation product, we considered that the structure **7** might better accommodate the reported preparation in high yield and properties of the dimer. This structure would arise from **2** by dehydration *via* **3** and retro-Claisen cleavage of the cyclohexanedione ring.



6



7

More definite evidence for **7** as opposed to **6** was obtained as follows. A *p*-bromophenacyl ester was prepared which analyzed correctly for a monocarboxylic

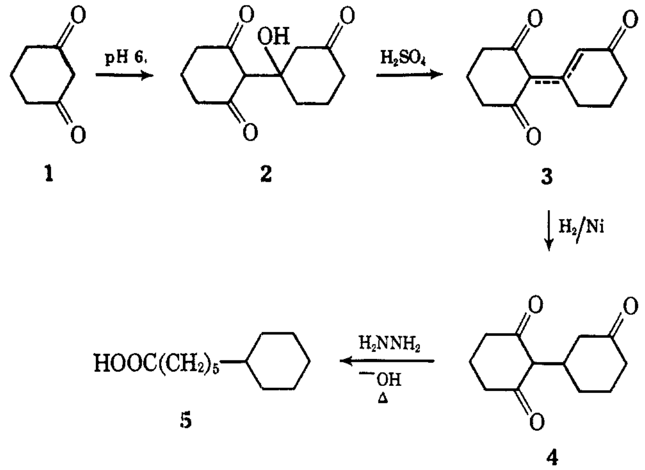
[1] Presented at the Midwest Regional American Chemical Society Meeting, Nov 4, 1965.

[2] H. Stetter, E. Siehnhold, E. Klauke, and M. Coenen, *Chem. Ber.*, **86,** 1308 (1953).

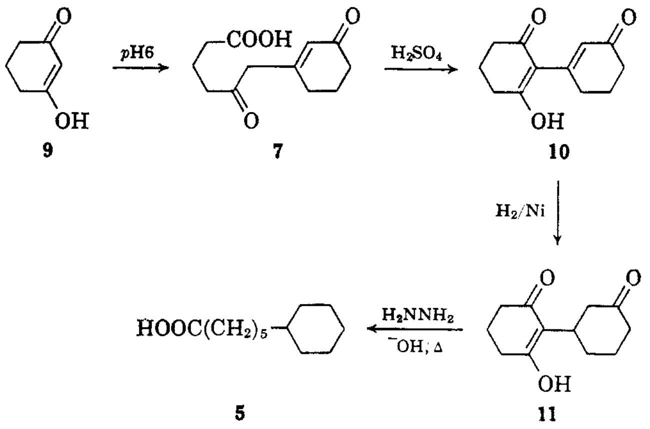
[3] K. Conrow and P. C. Radlick, *J. Org. Chem.*, **26,** 2260 (1961).

[4] S. Eskola, A. Auvinen, A. Hirvimies, T. Rinne, and R. Waris, *Suomen Kemi*, **27B,** 88 (1954).

Scheme I

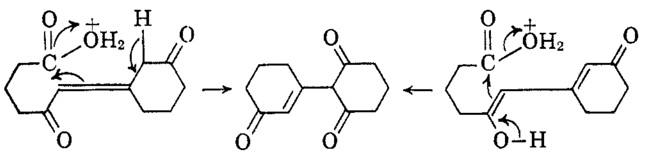


Scheme II



acid derivative. Pmr spectra of the dimer showed presence of vinyl hydrogen at about τ 4.2 and of the carboxylic acid proton at about τ −0.6 in deuteriochloroform. The ferric chloride test on the dimer was negative, though positive on dihydroresorcinol itself, indicating that there is no enol function present in the dimer and that the dimer is not cleaved to the starting material under the conditions of the ferric chloride test. Attempts to prepare an acetate of the hydroxyl function present in formulations **2** and **6** were never successful.

The dehydration product appears on the basis of its nmr spectrum (see Experimental Section) to be correctly formulated by Stetter. Reclosure of the second ring when **7** is treated under strongly acidic conditions is readily accommodated by either of the following mechanisms. The rest of the transformations and the ultimate proof of structure then proceed (ignoring tautomerism) as already formulated.



These ideas, combined with spectral evidence (see below) which bears on the tautomeric conditions of the compounds, permit the reformulation of the reaction sequence in Scheme II.

Since we had come to the conclusion that ring opening and ring closure had occurred in two successive steps which otherwise would present quite a simple reaction sequence, we felt compelled to provide more rigorous proof of the presence of the assigned functional groups than would usually be required. Accordingly we turned to an investigation of the changes in spectral properties with pH and to determination of the pK_a of the compounds. In addition to providing more definite proof of the correctness of the above reassignments, this work gave some results which are interesting in their own right.

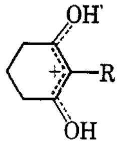
The ultraviolet spectrum, $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ϵ 4.14), of the dimer indicates that the double bond of **7** must be positioned endocyclic in the six-membered ring where Woodward's rules indicate an expected absorption maximum at 239 mμ. If the double bond were in the alternate position, exocyclic to the six-membered ring and conjugated with the other carbonyl group, the absorption maximum should appear at 244 mμ.

When the dimer **7** is exposed to aqueous dicarbonate solution, carbon dioxide evolution is observed and solution occurs. This does not, by itself, indicate the presence of a carboxylic acid functional group in the molecule since both cyclohexane-1,3-dione (**9**) and the dehydrated dimer **10** give this same reaction. However, the aqueous bicarbonate solution has an ultraviolet spectrum, $\lambda_{\max}$ 242 (log ϵ 4.16), which is essentially unchanged from that of the neutral ethanolic solution of dimer. Only upon exposure to more concentrated base does the absorption spectrum change markedly and an intense absorption at $\lambda_{\max}^{2N\mathrm{NaOH}}$ 397 mμ (log ϵ *ca.* 4.6) appears. This clear indication that there are two independent acidic functions in the dimer, only one of which, the less acidic, is involved with the chromophore, is evidence in favor of the structure **7** and rules out structures **2** and **6**.

Determination of the neutralization equivalent of the dehydrated dimer **10** shows that there is only a single acidic function in this substance. The spectra of the dehydrated dimer in solutions of different acidity indicate that this function influences the absorption spectrum. Solutions in ethanol (or dilute aqueous acid) have $\lambda_{\max}$ 268 mμ (log ϵ 4.14) with a shoulder at 236 mμ (log ϵ 4.06) which correspond to the enolic cyclohexanedione ring and the cyclohexenone ring absorbing as separate chromophores. In agreement with the spectral indication that the cyclohexanedione ring is enolic, the ferric chloride test gives a weak olive-gray color. In neutral or basic aqueous solution, the spectrum separates into two distinct peaks, one at 286 mμ (log ϵ 4.34), ascribed to the enolate ion, and the other at 238 mμ (log ϵ 4.04), attributed to the independent cyclohexenone chromophore. Since the enolate spectrum is already fully developed in bicarbonate solution, the enol must be the functional group responsible for the acidity of the dehydrated dimer to bicarbonate solution. That is, there is no longer a carboxylic acid group present in the dehydrated dimer.

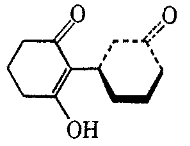
The hydrogenated dehydrated dimer **11** has only a single absorption maximum, $\lambda_{\max}^{\mathrm{EtOH}}$ 264 mμ (log ϵ 4.21), which is sensitive to the acidity of the medium, $\lambda_{\max}^{2N\mathrm{NaOH}}$ 290 mμ (log ϵ 4.40). These observations confirm the hydrogenation of the double bond in the cyclohexeneone ring and the assignment of the absorption bands in **10**, and indicate that **11** exists to a considerable extent in the enol form in solution.

During the determination of the absorption curves of these compounds in various solutions, it was noted that in strongly acidic solutions, the spectra again change, though by a smaller amount than in basic solutions. This change probably arises from protonation of the carbonyl oxygen of the enol to give a symmetrical conjugate acid **12**. The small magnitude of the change in absorption made determination of an acidity constant difficult, but the pK_a of the conjugate acid of dehydrated dimer **10** is about -1.3, in the same region as that reported for other cyclohexanedione derivatives.[5] This basicity of the dehydrated dimer helps to explain the success of the dehydration reaction in effecting reclosure of the six-membered ring: the product **10** is far more basic than the starting material **7**. Similarly, the necessity for neutralizing the dehydration mixture before extraction with chloroform (see Experimental Section, ref 2) is explained: in concentrated sulfuric acid the dehydrated dimer exists as the conjugate acid salt and is not extracted.



12

The spectra of the dehydrated dimer **10** show that the two chromophoric systems are independent of one another, even though they are formally conjugated. This fact indicates that the two cyclohexane rings lie in essentially perpendicular planes (**13**). This circumstance is not surprising in view of the similarity of the molecular system to that of 2,6-disubstituted biphenyls. The failure of the dimer **7** to exist as an enol and to be strongly acidic even though it is a vinylogous β-diketone may be understood on a similar basis. In the extended enol or enolate ion **14** coplanarity would cause a high degree of steric compression between the ring atoms adjacent to the point of attachment of the side chain and some portion of the side chain. In the diketo form **7** the side chain is free to rotate into a position where steric compression is minimized so dimer exists in the less crowded and less acidic noncoplanar diketo form.



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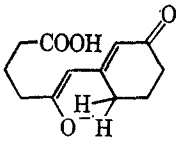

14

Since resonance stabilization of the enolate of **10** by conjugation with the cyclohexenone substituent is ruled out by the geometry of the system (as evidenced by the separate absorption of the two chromophores even in basic solution) the acid-strengthening effect of the unsaturated substituent in **10** is principally an inductive effect. In the hydrogenated material **11** the substituent is saturated so the difference in the acidities of the two substances should be an approximate measure of the difference in the inductive effects of unsaturated and saturated carbon free of contribution from a resonance effect. The size of the unsaturated and the hydrogenated substituents are virtually identical, so differences in solvation should make little or no contribution to the acidity difference.

In view of this theoretical point, the pK_a's of these two compounds were determined by spectrophotometric means,[6] using solutions in buffers of appropriate pH. The dehydrated dimer **10** has a pK_a of 4.4 and its hydrogenation product **11** has a pK_a of 8.3. The inductive effect of the unsaturated *vis-à-vis* the saturated substituent thus accounts for an acid-strengthening effect of nearly four orders of magnitude. This effect may be compared to that measured by Wepster in a comparison of quinuclidine and benzoquinuclidine, whose pK values differ by 2.73.[7] It is interesting to speculate on the reasons an enolate is apparently more sensitive to electron-withdrawing effects than an amino nitrogen is, assuming one observation can be taken as a trustworthy indication that this is so.

The possibility existed that the large ΔpK_a value between **11** and **10** was in part due to an intramolecular hydrogen bond in **11** not present in **10** because of the greater rigidity of the cyclohexene system. This would have the effect of reducing the acidity of **11** relative to **10** and thus increasing the ΔpK_a value. Accordingly, the infrared spectra of **11** were investigated with reference to this point. Nonhydrogen-bonded OH stretching absorption increases in intensity relative to hydrogen-bonded OH stretching absorption as increasingly dilute solutions in carbon tetrachloride were used. The most dilute solution showed no trace of hydrogen-bonded hydroxyl, though other peaks in the spectrum were still strong, so we may conclude that hydrogen bonding is not a factor in the decreased acidity of **11** as compared to **10**.

The pK_a of the enedione system of the dimer was determined spectrophotometrically and found to be 10.8. Two compounds with identical functional systems have had their pK_a determined, glutaconic dialdehyde, p$K_a = 5.75$, and 4-methyl-3-heptene-2,6-dione, p$K_a = 11.18$.[8] The large difference in pK_a of the two model compounds must be due to a combination of the electron-releasing effect of the methyl groups of the ketone in comparison to the hydrogen atoms of glutaconic dialdehyde and the increased steric compression in a coplanar conformation of the ketone. An additional effect in the dimer is the acid-weakening influence of the carboxylate function produced in the first dissociation of the dimer molecule. These effects cannot be sorted out with the limited data at hand, so one cannot say to what extent the acidity of enedione system is weakened by steric hindrance to coplanarity.

Experimental Section

Analyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Melting points were determined on a Fisher-Johns melting point block.

6-(3-Ketocyclohexyl)-5-ketohexanoic Acid (7).—Stetter's preparation using a pH 6 buffer for the dimerization was modified

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[5] E. M. Arnett, "Progress in Physical Organic Chemistry," Vol. I, S. B. Cohen, A. Streitwieser, Jr., R. W. T. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 364.

[6] P. Bladon, "Physical Methods in Organic Chemistry," J. C. P. Schwarz, Ed., Holden-Day, Inc., San Francisco, Calif., 1964, pp 161–163.

[7] B. M. Wepster, *Rec. Trav. Chim.*, **71**, 1159, 1171 (1952).

[8] J. F. King, "Technique of Organic Chemistry," Vol. XI, K. W. Bentley, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 357, 358.

on the basis of a calculation of the buffer capacity of the solutions used as compared to the quantity of dihydroresorcinol. Since it appeared that the buffering action was principally due to dihydroresorcinol and its salt, a mixture of 20.0 g (178 mmoles) of dihydroresorcinol and 7.5 g (89 mmoles) of sodium bicarbonate in 80 ml of water were heated under reflux 8 hr before the cooled solution was acidified and extracted with chloroform. The chloroform extracts were extracted with 5% sodium bicarbonate solution; the extracts were acidified, heated to boiling, decolorized with charcoal, filtered, and permitted to cool. Yellow crystals, 9.8 g (49%), collected and were recrystallized from 1 *N* hydrochloric acid to give colorless crystals, mp 95.5–97.5° (lit.[2] mp 98°), which show a tendency to darken while drying. The compound reacts with potassium permanganate in acetone and with bromine in chloroform–carbon tetrachloride, but does not give a color with ferric chloride in aqueous dioxane: ultraviolet, $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ε 4.14), $\lambda_{\max}^{5\%\,\mathrm{NaHCO_3}}$ 242 (4.16), $\lambda_{\max}^{2N\,\mathrm{NaOH}}$ 397 (*ca.* 4.7); nmr (τ values, in $CDCl_3$, integral in parentheses), −0.56 (*ca.* 1), -COO*H*, shifting upfield with addition of dioxane; 4.05 (0.96), vinyl H; 6.62 (2.04), 6-protons; 7.26–7.72 (8.00), 2,4,4′- and 6′-protons; and 7.92–8.23 (3.96), 3,5′-protons.

The *p*-**bromophenacyl ester** was prepared from 0.50 g (2.2 mmoles) of dimer and 0.64 g (2.3 mmoles) of *p*-bromophenacyl bromide in the usual manner.[9] Recrystallization from aqueous ethanol gave light green crystals, mp 103.5–104.5°.

Anal. Calcd for, $C_{20}H_{21}BrO_5$: C 57.02; H, 5.02; mol wt, 421. Found: C, 56.84; H, 5.07; mol wt, 426 (vapor pressure osmometer).

2-(3-Ketocyclohexenyl)cyclohexane-1,3-dione (**3** ⇌ **10**).—Preparation of the dehydrated dimer followed the method of Stetter, except that recrystallization was effected by dissolving the compound in chloroform and inducing crystallization by dilution with dioxane: mp 151–155° (lit.[2] mp 155°) with darkening; ultraviolet, $\lambda_{\max}^{\mathrm{EtOH}}$ 268 mμ (log ε 4.14), λ_{sh} 236 (4.06), $\lambda_{\max}^{6N\,\mathrm{H_2SO_4}}$ 273 (4.19), λ_{sh} 242 (4.09), $\lambda_{\max}^{\mathrm{H_2O}}$ 284 (4.21) and 239 (4.07), $\lambda_{\max}^{\mathrm{NaHCO_3\ or\ NaOH}}$ 286 (4.34) and 238 (4.04); nmr, −0.21 (*ca.* 1), enol H, shifting upfield upon addition of dioxane; 4.06 (0.88), vinyl H; 7.46–7.56 (8.05, a rough doublet), 4,6,4′,6′-protons; 7.88–7.96 (4.09, a rough doublet), 5,5′-protons. The neutralization equivalent was determined to be 202 *vs.* the phenolphthalein end point (theory 206).

2-(3-Ketocyclohexyl)cyclohexane-1,3-dione (**4** ⇌ **11**).—Hydrogenated dehydrated dimer was prepared by hydrogenation of the dehydrated dimer with Pd–C in glacial acetic acid at 3 atm of hydrogen pressure. The product, after removal of the catalyst and acetic acid, was crystallized from ethyl acetate: mp 166.5–167.5° (lit[2] mp 168°); ultraviolet, $\lambda_{\max}^{\mathrm{EtOH}}$ 264 mμ (log ε 4.21), $\lambda_{\max}^{6N\,\mathrm{HCl}}$ 278 (4.39), $\lambda_{\max}^{2N\,\mathrm{NaOH}}$ 290 (4.40); nmr, 4.55 (enolic -OH, shifting to higher field upon addition of dioxane), 6.82 (H at 2), 7.33–7.83, 7.83–8.37, and 8.37–8.75. The integration suggested the presence of a mixture of **4** and **11** in the nmr sample.

Determination of pK_a.—Sorensen's glycine–NaOH buffer[10] was used in the determination of the pK_a of dimer and hydrogenated dehydrated dimer and citrate buffers[10] for the determination of the pK_a of dehydrated dimer. For dimer, optical densities at 397 mμ were plotted *vs.* pH, and the pH of half-development of the maximum absorption was found to be 10.8.

For dehydrated dimer, plots of optical density *vs.* pH at 263 and 286 mμ were made and found to have inflection points at 4.35 and 4.52 pH units, respectively. An average value of 4.4 is taken as the pK. A plot of the ratio of optical density at 260 to that at 270 *vs.* H_0 of a series of different concentrations of hydrochloric acid gave a barely defined inflection at H_0 −1.3 for the dehydrated dimer conjugate acid.

Since the buffer range of glycine–sodium hydroxide buffer did not extend to acidic enough solutions to define a whole titration curve, the pK_a of hydrogenated dehydrated dimer was calculated[6] on the observed absorbances at 266 and 288 mμ at three pH values. The mean of the pK values so calculated was 8.25 ± 0.07 (average deviation).

Acknowledgment.—The National Institutes of Health (GM 11013) provided financial support; the A-60 nmr spectrometer was purchased with the aid of an equipment grant from the National Science Foundation. Mr. Kenneth Wolma prepared samples of dimer and did some exploratory work on its structure.

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[9] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 200.

[10] "International Critical Tables," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1926, pp 82, 83.

Systems with Bridgehead Nitrogen. β-Ketols of the 1-Azabicyclo[2.2.2]octane Series

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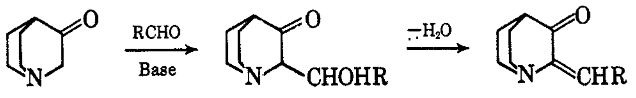
Received November 29, 1965

The preparations and chemical behavior of the first β-ketols incorporating the 1-azabicyclo[2.2.2]octane ring are described. Three different structural types are represented in this study. Methylolation of 3-quinuclidinone (**1**) with excess formaldehyde (potassium carbonate catalyst under appropriate conditions) led to 2,2-bismethylol-3-quinuclidinone (**4**) or 2-methylene-3-quinuclidinone (**3c**). 2-Methylol-3-quinuclidinone (**2c**) was prepared by hydration of **3c** cation. Starting with 4-acetylpiperidine and its N-benzyl derivative, syntheses of 4-hydroxymethyl-3-quinuclidinone (**17**) and 4-acetyl-3-quinuclidinol (**26**) were achieved. The bridgehead methylol compound **17** was found to be extremely stable whereas **26** underwent facile retrograde aldolization in basic media. The bismethylol derivative (**4**) readily loses one methylol group in base leading to ketol **2c**, which dehydrates with extreme ease rather than undergo demethylolation.

Although numerous derivatives of 1-azabicyclo[2.2.2]octane (quinuclidine) are known, none incorporating a β-ketol structure appear to have been described previously.[1] 3-Quinuclidinone (**1**) has been condensed with benzaldehyde[2,3] and quinoline-4-carboxaldehyde[3] to produce α,β-unsaturated ketones **3a** and **3b**, respectively. However, the β-ketol precursors **2a** and **2b** have not been isolated. In the present study three β-ketols of the quinuclidine series, each of a different type (including **2c**, R = H), have



1 **2** **3**

a, R = C_6H_5
b, R = 4-quinolyl
c, R = H

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[1] (a) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen," Part 2, Interscience Publishers, Inc., New York, N. Y., 1961, pp 1331–1356; (b) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, in press.

[2] V. Braschler, C. A. Grob, and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963).

[3] G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).