The Structure of "Acetone Anil," 2,2,4-Trimethyl-1,2-dihydroquinoline

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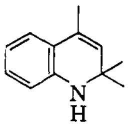
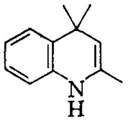
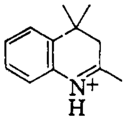
The condensation product of aniline with two molar equivalents of acetone has been given the trivial name "acetone anil" although it is in fact a dihydroquinoline. The weight of evidence favors the structure 2,2,4-trimethyl-1,2-dihydroquinoline (I), but an alternative 2,4,4-trimethyldihydroquinoline formulation (II) has not been rigorously excluded from consideration as the structure of "acetone anil."[1] Ultraviolet spectroscopy has been used to support the assignment of structure I; Johnson and Buell[2] have pointed out the similarity of the ultraviolet spectrum of "acetone anil" to that of *o*-aminostyrene and have concluded that structure I is correct. Craig and Gregg[3] have criticized the validity of this argument on the grounds that the ultraviolet spectrum of "acetone anil" does not eliminate the possibility that the compound is a 1,4-dihydroquinoline derivative;[4] they considered, however, that the similarity of its ultraviolet spectrum in acid solution to those of 1,2-dihydronaphthalene and its 4-methyl derivative provided compelling evidence for the 1,2-dihydroquinoline structure, I. It may be pointed out in turn that the evidence from the ultraviolet spectrum in acid solution is itself ambiguous in that, were "acetone anil" a 1,4-dihydroquinoline derivative, protonation would be expected to occur on carbon[8,9] giving a species, III, whose spectrum might resemble that observed. As the structure of "acetone anil" was of interest to us in connection with another investigation, we have attempted to accumulate further evidence on which to base a decisive choice between I and II.



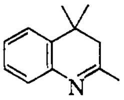
I



II



III



IV

The infrared spectrum of "acetone anil" in chloroform solution shows a medium strength NH band at 2.95 μ. Witkop's results in connection with imine-enamine tautomerism[9] indicate that, were "acetone anil" a 2,4,4-trimethyldihydroquinoline, the imine form IV would largely predominate and only a very weak NH band would be observed. Further, the band of "acetone anil" at 6.04 μ, which is absent in the spectrum of its hydrogenation product and may be assigned to the double bond, is not shifted to lower wave lengths in the spectrum of "acetone anil" hydrochloride. A compound of either structure II or IV would be expected to give rise to the protonated species III with concomitant shift of the double bond band to shorter wave lengths.[8,9] Thus the infrared data favor structure I for "acetone anil."[10]

The proton magnetic resonance spectra for "acetone anil" and its acetyl and dihydro derivatives have now been recorded.[11] "Acetone anil" shows, in addition to the series of peaks due to the aromatic hydrogen atoms, four bands with τ values[12]; 4.78, 6.40, 8.06 (doublet, J $\sim$ 1.0 c/s.) and 8.81; the areas of these bands were in the approximate ratio 1:1:3:6. They may be assigned respectively to the vinyl, amine, single methyl, and *gem*-dimethyl hydrogen atoms of *either* I *or* II; but cannot be interpreted in terms of structure IV. In accordance with these assignments the band in the $\tau = 6.4$ region is absent in the spectrum of the acetyl derivative, while a new singlet appears in the $\tau = 8.0$ region which is attributable to the hydrogen atoms of the acetyl group. Also, the dihydro compound fails to show a band in the $\tau = 4.5$–5.0 region, and shows a new, highly split multiplet centered about $\tau = 7.1$, which may be assigned to a single hydrogen at the 4-position of I (or the 2 position of II), together with other changes in the region $\tau = >8.0$. Unfortunately, these spectra do not permit a choice between I and II.

Although the spectral evidence taken as a whole favors structure I, we considered it important to seek chemical evidence in addition. Earlier experiments directed towards the oxidative degradation of "acetone anil" led to unidentified products.[13] The acetyl derivative of "acetone anil" has now been oxidized with the permanganate-periodate

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(1) See D. Craig, *J. Am. Chem. Soc.*, **60**, 1458 (1938), for leading references to early work.

(2) W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, **74**, 4517 (1952).

(3) D. Craig and E. C. Gregg, Jr., *J. Am. Chem. Soc.*, **75**, 2252 (1953).

(4) It may be noted, however, that the spectra of compounds considered to be 1-methyl-4-cyano-1,4-dihydroquinoline[5] [λ_{max} 230 mμ (log ϵ 3.93); 302 mμ (log ϵ 3.95)] and 1-methyl-4-(α-cyano-α-aralkyl)-1,4-dihydroquinolines[6] are markedly different from those of "acetone anil" and other compounds which have been assigned 1,2-dihydroquinoline structures.[2,7] Nevertheless, this cannot be considered as decisive, as the position of the double bond in these presumed 1,4-dihydroquinoline derivatives has not been proved unequivocally.

(5) A. Kaufmann and A. Albertini, *Ber.*, **42**, 3776 (1909).

(6) N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.*, **74**, 3671 (1952).

(7) K. Sutter-Kostič and P. Karrer, *Helv. Chim. Acta*, **39**, 677 (1956).

(8) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(9) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

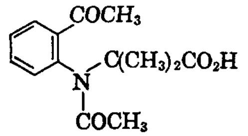
(10) The possibility that I might protonate on carbon cannot be completely eliminated and thus this conclusion is still not completely rigorous. However, such protonation would appear *a priori* less likely for I than for II.

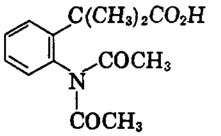
(11) We thank Mr. T. J. Curphey for these measurements.

(12) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

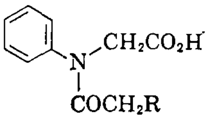
(13) P. Kalnin, *Ann.*, **523**, 118 (1936).

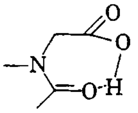
reagent[14] to give a crystalline product, m.p. 194–195°, with the formula $C_{14}H_{17}NO_4$. This product could be either V or VI, derived from I or II, respectively. A choice can be made between these

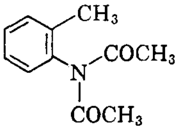

V


VI

possibilities on the basis of the fact that the oxidation product gives a positive iodoform test, showing it to have structure V. The infrared spectrum (Nujol) of the oxidation product confirms this structural assignment, having bands at 5.71 μ (carboxylic acid), 5.89 μ (aromatic ketone), and 6.17 μ (tertiary amide). These may be compared with the bands of *N*-acetyl-*N*-phenylglycine (VII) at 5.75 μ (carboxylic acid) and 6.18 μ (tertiary amide)[15] and of *N*-phenacetyl-*N* phenylglycine (VIII) at 5.71 μ (carboxylic acid) and 6.11 μ (tertiary amide).[16] The combination of the unusually low wave length of the carboxylic acid bands and the unusually high wave length of the amide bands[17] in the spectra of these compounds may be interpreted in terms of *monomeric* structures, with intramolecular hydrogen bonding between the carboxylic acid and the amide carbonyl groups (*cf.* IX).[18] The infrared spectrum of the oxidation product is not, however, in accord with structure VI. Thus, the *N*,*N*-diacetyl derivative of *o*-toluidine, X, shows a poorly resolved doublet in its spectrum at 5.78–5.83 μ,[19] while the amide band in the spectrum of the oxidation product falls at a considerably longer wave length.[20] The structure of "acetone anil" is therefore established as I.[21]


VII. R = H
VIII. R = C_6H_5


IX


X

EXPERIMENTAL[22]

"Acetone anil" (I) was prepared by the method of Vaughan[23] and was obtained as a pale yellow oil, b.p. 131° (6 mm.) [lit.[23] b.p. 133–138° (13 mm.)]; $\lambda_{max}^{CHCl_3}$ 2.95, 6.04 μ; τ 4.78, 6.40, 8.06 (doublet, J ~ 1 c./s.), 8.81. The *hydrochloride* was prepared by the procedure of Craig[1] and after recrystallization from ethanol-ether had m.p. 212–213° (lit.[1] m.p. 212–213°); λ_{max}^{Nujol} 6.04 μ. The *acetyl derivative* was prepared by the method of Cliffe[24] and was obtained as a yellow oil, b.p. 172° (18 mm.) [lit.[24] b.p. 175° (23 mm.)], which slowly solidified; recrystallization of the solid from petroleum ether gave yellow prisms, m.p. 54–55° (lit.[24] m.p. 54°); $\lambda_{max}^{C_2H_5OH}$ 243 mμ (log ε 4.41), 285 mμ (log ε 3.63); $\lambda_{max}^{CHCl_3}$ 5.98 μ; τ 4.65, 8.03, 8.13, 8.63.

Dihydro derivative of "acetone anil." A solution of 2.09 g. (0.01 mole) of the hydrochloride of "acetone anil" in 125 ml. of ethanol was hydrogenated at atmospheric pressure over platinum. The catalyst was filtered and the solution was concentrated to afford 1.7 g. of colorless prisms, m.p. 207–209°; a mixture melting point with the starting material was depressed. The product was dissolved in water and treated with dilute aqueous sodium hydroxide. The resulting suspension was extracted with ether, and the ether solution was evaporated to leave an oil which slowly crystallized at 0°. Recrystallization of the solid gave the dihydro derivative of "acetone anil" as colorless prisms, m.p. 42–43° (lit.[25] m.p. 41°); $\lambda_{max}^{C_2H_5OH}$ 248 mμ (log ε 4.03), 302 mμ (log ε 3.42); $\lambda_{max}^{CHCl_3}$ 2.94 μ; τ 6.60, 7.10 (multiplet), 8.33, 8.58, 8.78, 8.85.

Hydrogenation of the acetyl derivative of "acetone anil." A solution of 2.15 g. of the acetyl derivative of "acetone anil" in 125 ml. of ethanol was hydrogenated at atmospheric pressure over platinum. The reduction was stopped after the uptake of 1.1 molar equivalents of hydrogen. The solution was filtered from the catalyst and evaporated to small volume. The residual oil solidified after storage in a vacuum desiccator. The solid was recrystallized from petroleum ether to give the dihydro compound as flat, colorless prisms, m.p. 87–88°; $\lambda_{max}^{C_2H_5OH}$ 210 mμ (log ε 4.31), 253 mμ (log ε 4.09); $\lambda_{max}^{CHCl_3}$ 6.05 μ.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.63; H, 8.92; N, 6.40.

Oxidation of the acetyl derivative of "acetone anil": Formation of V. To 15 g. of potassium periodate stirred in 600 ml. of water was added 0.4 g. of potassium permanganate, 5 g. of potassium carbonate, and 3 g. of the acetyl derivative of "acetone anil." The reaction mixture was stirred for 5 hr.; it was then treated with sodium bisulfite until the color of the solution became light yellow and extracted with ether containing a small quantity of dichloromethane until the organic layer was colorless. The extract was evaporated to a dark oil, and this was redissolved in ethanol. On being cooled and scratched the solution slowly deposited 0.2 g. of

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(14) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33,** 1701 (1955); E. von Rudloff, *Can. J. Chem.*, **34,** 1413 (1956).

(15) A. Gierer, *Z. Naturforsch.*, **86,** 654 (1953).

(16) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949, p. 155.

(17) Tertiary amides with a phenyl group on the nitrogen atom usually absorb *ca.* 5.92 μ: L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd., London, 2nd ed., 1958, p. 213.

(18) Similar interpretations have been made of anomalies in the spectra of *o*-methoxy aromatic carboxylic acids: S. Marburg, Ph.D. thesis, Harvard, 1960; J. W. Huffman, *J. Org. Chem.*, **24,** 1759 (1959); *cf.* E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, **75,** 4585 (1953).

(19) For the infrared spectra of other compounds of this type, see B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74,** 3861 (1952); F. C. Uhle, C. M. McEwen, Jr., H. Schröter, C. Yuan, and B. W. Baker, *J. Am. Chem. Soc.*, **82,** 1200 (1960).

(20) Hydrogen bonding of this type illustrated in IX would not be expected for VI since this would require the formation of a much larger ring. Intramolecular hydrogen bonding of the carboxylic acid with the nitrogen atom in VI would tend to lower, rather than to raise, the wave length of the amide band relative to the wave lengths of the amide bands of X.

(21) Other chemical evidence has been adduced very recently in favor of this structure: J. P. Brown, *Chem. & Ind.*, 233 (1960).

(22) Melting points and boiling points are uncorrected.

(23) W. R. Vaughan, *Org. Syntheses*, Coll. Vol. **III,** 329 (1955).

(24) W. H. Cliffe, *J. Chem. Soc.*, 1327 (1933).

(25) G. Reddelien and A. Thurm, *Ber.*, **65,** 1511 (1932).

colorless crystals which were collected and washed with ether. This product melted at 187°; after several recrystallizations from alcohol and passage through a column of alumina, it had m.p. 194–195°; $\lambda_{\max}^{\text{Nujol}}$ 3.75–3.95, 5.71, 5.89, 6.17 μ.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.35; N, 5.54.

Diacetyl derivative of o-toluidine (X). This was prepared by the method of Sudborough[26] and obtained as an oil, b.p. 142–143° (9 mm.) [lit.[26] b.p. 152–153° (20 mm.)]; $\lambda_{\max}^{\text{Nujol}}$ 5.78–5.83 μ (poorly resolved doublet).

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[26] J. J. Sudborough, *J. Chem. Soc.*, 79, 533 (1901).

Configurations of the Isophorone Oximes

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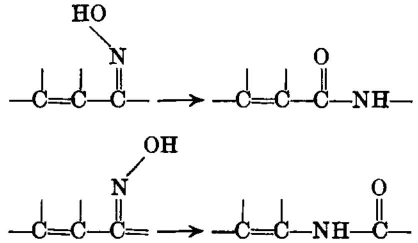
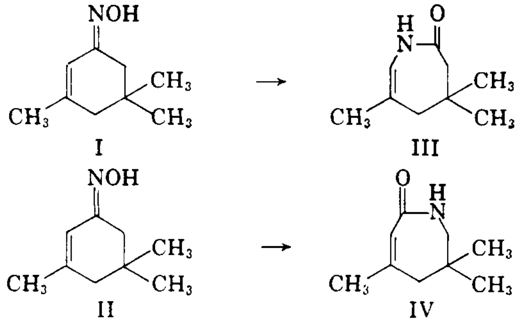
The Beckmann rearrangement has not only been a useful synthetic tool but has proved of great value in determining the configurations of *syn* and *anti* aldoximes and ketoximes.[1] Previous work has been virtually exclusively limited to the study of oximes of saturated carbonyl compounds with a few references to rearrangement of α,β-unsaturated ketoximes.[2–10] The latter type should be especially valuable for configuration determination since only an ultraviolet spectrum might be necessary to distinguish between the products. Thus, *syn*-α,β-unsaturated ketoximes lead to α,β-unsaturated amides or lactams while the *anti*-isomers give acylated enamines or enamine lactams. The two types of products might be expected to have markedly different ultraviolet absorption maxima but which should be reasonably constant from compound to compound. Also, if the unsaturated and saturated lactams and/or oximes can be related (reduction or oxidation), the configurations of the saturated oximes are simultaneously determined.



We attempted to use this method to assign the proper structure to a C-ring steroid lactam.[9] Although the isophorone (3,5,5-trimethyl-2-cyclohexenone) oximes and resulting lactams were excellent models for the steroid case from the standpoint of both ring size and substitution, the evidence which had been presented suggested that the configurations had been incorrectly assigned,[5] a premise shown to be true by the present work.

The existence of the two oximes of isophorone was a subject of controversy in the early chemical literature.[11–15] It was assumed[12,15] that their formation was due to a double bond isomer present in some preparations of isophorone. Apparently the concept[16] of *syn*- and *anti*-oximes was slow to gain acceptance. Finally, Montgomery and Dougherty[5] repeated the separation of the two isomers, demonstrated their interconvertibility, and isolated a Beckmann rearrangement product in low yield from each. We have repeated and confirmed this work and have greatly improved the yield in the Beckmann rearrangement of the *anti*-oxime by using the polyphosphoric acid method of Horning.[4]



That the two oximes were really *syn*- and *anti*-isomers of an α,β-unsaturated ketone was shown by their nearly identical ultraviolet spectra.[5] The additional question arises in a reaction proceeding in low yield as to whether the product truly represents the configuration of the starting material. However, when a good yield is obtained, either the product is related directly to the starting material or isomerization of the starting material is essentially complete before reaction takes place. Since, in the

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[1] A. H. Blatt, *Chem. Rev.*, 12, 215 (1933); B. Jones, *Chem. Rev.*, 35, 335 (1944).

[2] A. H. Blatt and J. F. Stone, Jr., *J. Am. Chem. Soc.*, 53, 4134 (1931).

[3] R. C. Morris and A. V. Snider, U. S. Patent 2,462,009 (Feb. 15, 1949).

[4] E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, 74, 5153 (1952).

[5] R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, 17, 823 (1952).

[6] C. S. Barnes, D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 2339 (1952).

[7] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 21, 520 (1956).

[8] F. J. Donat and A. L. Nelson, *J. Org. Chem.*, 22, 1107 (1957).

[9] R. H. Mazur, *J. Am. Chem. Soc.*, 81, 1454 (1959).

[10] J. Romo and A. Romo de Vivar, *J. Am. Chem. Soc.*, 81, 3446 (1959).

[11] E. Knoevenagel, *Ann.*, 297, 185 (1897).

[12] J. Bredt and R. Rübel, *Ann.*, 299, 160 (1898).

[13] W. Kerp and F. Müller, *Ann.*, 299, 193 (1898).

[14] L. Wolff, *Ann.*, 322, 351 (1902).

[15] A. W. Crossley and C. Gilling, *J. Chem. Soc.*, 95, 19 (1909).

[16] A. Hantzsch and A. Werner, *Ber.*, 23, 11 (1890).