Spectroscopic Studies of Keto–Enol Equilibria. VI. β-Ketoamides and β,β-Diketoamides[1]

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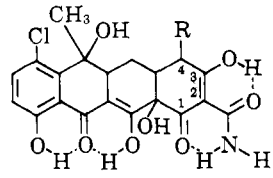
Model compounds for the diketoamide portion of aureomycin have been investigated by both p.m.r. and infrared spectroscopy. Systems such as 2-carbamoyl-5,5-dimethylcyclohexane-1,3-dione are enolic with very strong hydrogen bonds. Some of the factors responsible are explored.

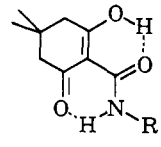
Some evidence has appeared for the highly enolic character of the diketoamide grouping in tetracycline antibiotics. For example in crystal studies of aureomycin [I, R = $N(CH_3)_2$], Donohue and his collaborators[2] found abnormal bond lengths in the amide function (C-2). They suggested that one of the chelated protons was attached to the amide oxygen resulting in two keto functions at C-1 and C-2. The high acidity of the enolic proton of the diketoamide moiety is another suggestion



I, R = H and $(CH_3)_2N$

for the extensive electron delocalization in the system.[3] Hence the pK_a of the acidic proton of the dicarbonyl–amide system is 5.97 in dedimethylaminotetracycline (I, R = H), but, with the dimethylamino group present [I, R = $N(CH_3)_2$] as in aureomycin, the pK_a was found to be 3.30.

We wish to present here spectroscopic evidence (both infrared and proton resonance) relevant to the diketoamide portion of the aureomycin and in agreement with the findings of Donohue and his collaborators. Since the plethora of functional groups and exchangeable hydrogens in the complete tetracycline molecule render them difficult to study by the usual spectroscopic procedures, simpler model systems derived from dimedone (5,5-dimethylcyclohexane-1,3-dione) were utilized. The



II, R = H and CH_3

models embodied the diketoamide grouping (II) with no other interfering functional groups, and proved to be interesting molecules in their own right. For purposes of comparison, several other aliphatic and dimedone derivatives were also studied.

Experimental

Proton Resonance Spectra.—Spectra were taken on a Varian A-60 spectrometer operating at 60.00 Mc. (sample temperature 31°). The reference zero was internal tetramethylsilane and the chemical shifts are given in p.p.m. downfield from this point (δ-scale). The spectra were calibrated by extrapolation from an adjacent side band of TMS generated by an audio oscillator. The stability of the spectrometer renders the usual procedure of interpolating between two side bands unnecessary (the accuracy of the sweep circuit was also checked). The oscillator was continuously monitored by a frequency counter. The data are good to 0.3 c.p.s. or 0.005 p.p.m. except when band width precluded such accuracy. All solutions were vacuum degassed and were 10% w./v. except when noted.

Infrared Spectra.—Spectra were obtained on a Perkin-Elmer Model 237 grating spectrometer. The instrument was calibrated with the aid of film polystyrene, and the wave lengths are accurate to 0.01 μ. Deuteration studies were performed by dissolving the compound in hot dioxane, precipitating it with deuterium oxide, and then drying the compound over phosphorus pentoxide. As a precaution, the spectra were taken in chloroform-*d*.

Solvents.—Chloroform-*d* and pyridine-d_5 were supplied by Merck Sharp and Dohme of Canada. Normal chloroform was freed from alcohol by shaking with several portions of alumina, then filtering through alumina. The remaining solvents were commercial reagent materials.

Compounds.—2-Carbamoyldimedone (2-carbamoyl-5,5-dimethylcyclohexane-1,3-dione) was synthesized by the procedure of Scarborough and Gould.[4]

2-Acetiminodimedone (2-acetimino-5,5-dimethylcyclohexane-1,3-dione) was synthesized from 2-acetyldimedone according to the directions of Crossley and Renouf.[5]

In a procedure similar to that for 2-carbamoyldimedone, N-methyl-2-carbamoyldimedone was prepared[6] by the fusion of dimedone and 1,3-dimethylurea at ~180°. The compound was repeatedly crystallized from cyclohexane or methanol, then fractionally sublimed several times (60°, 0.01 mm.), m.p. 129–131°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.49; H, 7.70; N, 7.04.

N-Methyl-2-acetiminodimedone was prepared from aqueous methylamine and 2-acetyldimedone. The material was crystallized from benzene–cyclohexane and then sublimed, m.p. 111.4–112.2°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.57; H, 8.76; N, 7.11.

N-Benzyl-acetoacetamide was prepared from diketene and benzylamine according to the procedure of Mukaiyama, *et al.*[7]

The preparation of ethyl N-benzyl-β-aminocrotonate was described previously.[1]

N-Methyl-4,4-dimethyl-3-oxovaleramide was produced by warming ethyl 4,4-dimethyl-3-oxovalerate with aqueous methylamine. The excess methylamine and water were removed *in vacuo* and the residue was crystallized several times from benzene–cyclohexane and then sublimed, m.p. 93–95°.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.88; H, 9.69; N, 8.93.

N-Benzyl-3(N-benzylamino)crotonamide was formed by adding 2 moles of benzylamine to 1 mole of diketene in benzene solution. The solution was refluxed for 1 hr. and the solvent was removed *in vacuo*. The residue was crystallized from benzene–cyclohexane, m.p. 102.5–104.5°.

(1) Part V: G. Dudek and G. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963).

(2) J. Donohue, J. Dunitz, K. N. Trueblood, and M. S. Webster, *ibid.*, **85**, 851 (1963).

(3) L. J. Leeson, J. E. Krueger, and R. A. Nash, *Tetrahedron Letters*, **No. 18**, 1155 (1963), and references contained therein.

(4) H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).

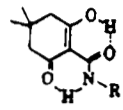
(5) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **101**, 1524 (1912).

(6) We wish to thank V. Georgian for suggesting this synthesis.

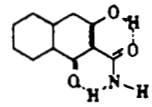
(7) T. Mukaiyama, M. Tokizawa, and H. Nohira, *J. Org. Chem.*, **26**, 4381 (1961).

TABLE I

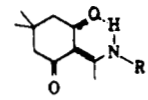
PROTON RESONANCE DATA[a] FOR COMPOUNDS OF THE TYPE



Solvent (concn., *M*)	R	Dimethyls	Methylenes		R	NH	OH
$CDCl_3$ (0.33)	H	1.09	2.35	2.48	6.0	9.3	17.77
(0.65)	H	1.08	2.35	2.48	6.2	9.4	17.79
C_5D_5N	H	0.92	2.41		9.6	9.9	18.7
Dioxane	H	1.03	2.28	2.45	7.2	9.3	18.2
CCl_4	CH_3	1.08	2.23	2.40	2.91 (5.1)[b]	9.6	18.15
$CDCl_3$	CH_3	1.08	2.33	2.46	2.92 (5.2)	9.7	18.13
C_6H_6	CH_3	0.67	2.05		2.43 (5.1)	9.8	18.78



Solvent	Methylenes[c]		NH_1	NH_1	OH
$CDCl_3$	1.5	2.5	5.9	9.6	17.84 18.04
C_5D_5N			9.8	10.3	18.98



Solvent	R	*gem*-Dimethyls	Methylenes	Methyls	R	NH
$CDCl_3$	H	1.04	2.38	2.56	7.4	12.1
C_5D_5N	H	1.15	2.48	2.72	9.7	12.3
Dioxane	H	0.98	2.28	2.44	7.6	11.9
$CDCl_3$	CH_3	1.03	2.36	2.57	3.08 (5.2)	13.3
CCl_4	CH_3	1.01	2.23	2.51	3.09 (5.1)	13.4

[a] In parts per million. [b] In cycles per second. [c] Broad and complex.

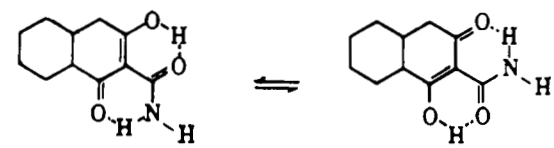
Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.20; H, 7.17; N, 9.96.

Results

P.m.r. Studies.—The proton resonance spectra ($CDCl_3$ solution) of 2-carbamoyldimedone (II, R = H) indicate that three acidic protons are present (Table I). Two give rise to broad signals at δ 6.3 and 9.5, respectively. The positions and shapes of these signals are very similar to the NH signals in several β-amino-α,β-unsaturated ketones.[1] The third acidic proton resonance appears at δ 17.8 with a line width which is narrow in comparison to the other two bands and is assigned to the enolic hydrogen. The presence of a signal at very low field is indicative of a strongly hydrogen-bonded, enolic system; the only other aliphatic systems giving rise to such low field resonances are those of the acetylacetone enols (δ 16) and the β-tricarbonyl enols (in 2-acetyldimedone, the enolic hydrogen is at δ 18.1).[8] In pyridine-d_5 solution, the higher field NH resonance is shifted markedly downfield owing to association with the basic solvent while the other two signals are less affected since they are already strongly chelated.

In N-methyl-2-carbamoyldimedone (II, R = CH_3), the N-methyl resonance is a 5.2-c.p.s. doublet with δ 2.92, the NH signals appear at 9.7, and the hydroxyl is at 18.1. The replacement of the amide hydrogen by a methyl group affects both the hydroxyl and the remaining amide hydrogen, shifting both resonance signals downfield.

(8) S. Forsen and M. Nilsson, *Acta Chem. Scand.*, **13**, 1383 (1959).



IIIa IIIb

The decalin analog[9] is similar in both infrared and proton resonance spectra to 2-carbamoyldimedone compound. The very low-field signal (δ 17.1) is split into a 0.2-p.p.m. doublet (Figure 1) which collapses in pyridine solution to a broadened singlet at δ 19.0. The doublet may result from a small chemical shift difference of the hydroxyl proton (IIIa or b). The ring protons were not analyzed since they give rise to featureless signals at δ 1.5 and 2.5.

A system related to the diketoamides is the Schiff base derived from ammonia and 2-acetyldimedone.[10] The compound could possess either structure IVa or b. The two methylene signals of the compound are equivalent in three solvents,[12] which implies that the second structure, the symmetric one, is preferred. This conclusion agrees with studies of anils formed from 2-

(9) We wish to thank Professor R. B. Woodward for the gift of this compound.

(10) Tetracyclines have been isolated with an aceto group in place of the amide function at C-2 (see I).[11] To date, no natural products have been isolated with the aceto group (at C-2) converted into a Schiff base by the action of ammonia, but their existence would not be unexpected.

(11) F. A. Hochstein, M. Schach von Wittenau, F. W. Tanner, and K. Murai, *J. Am. Chem. Soc.*, **82**, 5934 (1960); F. A. Hochstein and H. W. Miller, *J. Org. Chem.*, **27**, 2525 (1962).

(12) The 2-carbamoyldimedones show appreciable differences in chemical shifts of the two methylene groups (Table I).

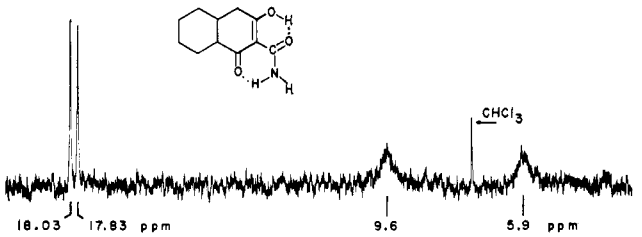


Figure 1.—P.m.r. spectrum chloroform-d solution, 60 Mc.) of the acidic protons of 2-carbamoyl-1,3-decalindione.

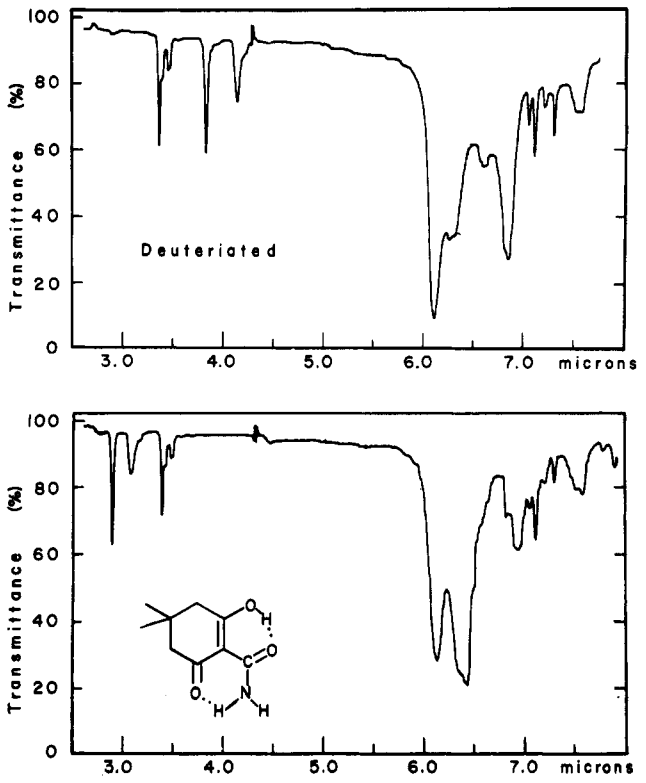
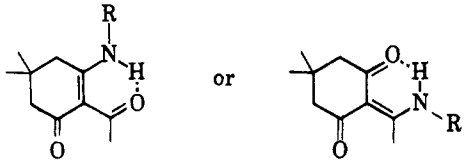


Figure 2.—Infrared spectra of deuterated and normal 2-carbamoyldimedone.

acetyldimedone and various anilines.[13] It should be noted that the second carbonyl shifts the resonance of the ethylidine methyl signal downfield compared with the methyl signal of several acetylacetone imines.[14]

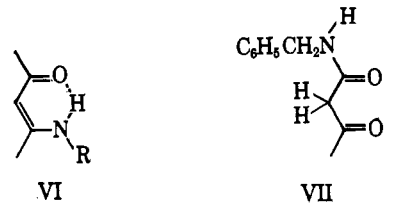


IVa or IVb, R = H and CH_3

The addition of methylamine to 2-acetyldimedone produces 2-(N-methylacetimino)dimedone (IVb, R = CH_3). The p.m.r. spectrum of this compound further confirms the symmetrical structure for the condensation products. In $CDCl_3$ solution, the N-methyl resonance is a 5-c.p.s. doublet at δ 2.57 and the NH signal appears at 13.3. This can be compared with δ 10.7 ($CDCl_3$ solution) for the NH signal in the acyclic N-methylacetylacetone imine (VI).[14]

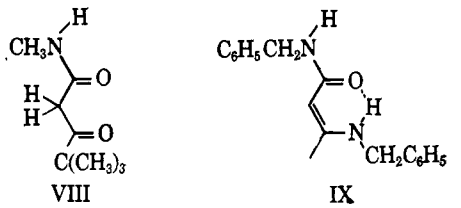
(13) G. M. Chopra and B. H. Iyer, *Current Sci.* (India), **22**, 206 (1953); *Chem. Abstr.*, **49**, 887 (1955).

(14) G. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1951).



VI VII

When there is only one carbonyl in the β-position to an amide, the compound is ketonic. In the p.m.r. spectra of N-benzylacetoacetamide (VII), the band at δ 3.37 (Table II), which could be either a high-field vinyl signal or a methylene resonance, integrates to two protons, while no trace of an enolic hydroxyl can be found at lower fields. Even in pyridine, the enol is not detectable. With ethyl 4,4-dimethyl-3-oxovalerate the normal sequence of reactivity in β-keto esters toward amines (keto > ester) is reversed, owing to steric hindrance of the keto function. Thus when ethyl 4,4-dimethyl-3-oxovalerate is warmed with aqueous methylamine, the ester function is converted to the amide (VIII) which possesses no ethyl signals in its p.m.r. spectrum but a resonance equivalent to two protons at δ 3.49 (due to the methylene signal).[15] When the previously studied[15] ethyl N-benzyl crotonate is compared with N,N'-dibenzyl crotonamide (IX), little change is noted.



VIII IX

Infrared Spectra.—The infrared spectrum of 2-carbamoyldimedone (II, R = H) contains both an associated and a free NH stretch, but as expected for a strongly hydrogen-bonded, enolic proton, no hydroxyl signal can be seen.[17] Upon deuteration of 2-carbamoyldimedone, the NH bands are replaced by ND bands at 2590 and 2410 cm.$^{-1}$ (Figure 2); the H–D shift is 1.34. Since deuteration of the enolic hydroxyl (confirmed by p.m.r. spectroscopy) failed to produce an infrared absorption in the 2400-cm.$^{-1}$ region, it is evident that the OH absorption has not been masked by the CH frequencies at 2900 cm.$^{-1}$ in the normal compound.

In the 1600-cm.$^{-1}$ region, 2-carbamoyldimedone possesses two strong infrared bands, one at 1639 and the second about 1563 cm.$^{-1}$. Deuteration shifts the 1563 band to 1458 cm.$^{-1}$, the low H–D ratio of 1.12 indicating the band is strongly coupled.[18] Beneath the 1563-cm.$^{-1}$ band, there is a second one which is readily seen in the spectrum of the deuterated material (Figure 2). In N-methyl-2-carbamoyldimedone (II, R = CH_3), the changes produced by deuteration are similar to those observed for 2-carbamoyldimedone. Further-

(15) A small amount of the enol form is present in both pyridine and benzene solutions for the *t*-butyl compound VIII. The ratio of keto to enol is about 10:1 in both these solvents. The ratios are small when compared to the parent β-keto esters. In inert solvents such as carbon tetrachloride, ethyl acetoacetate is about 30% enolic,[16] while benzyl acetoacetamide (VII) possesses an undetectable amount of the enol form as discussed above.

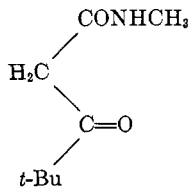
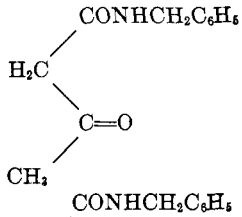
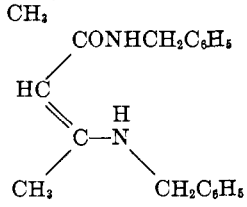
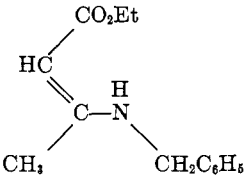
(16) C. Giessner-Prettre, *Compt. rend.*, **250**, 2547 (1960).

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, Chapter 12.2.

(18) R. N. Knisely, E. L. Farquhar, and L. S. Gray, *Spectrochim. Acta*, **18**, 1217 (1962). This reference has been given since it is also useful for infrared amide assignments.

TABLE II

PROTON RESONANCE DATA FOR ALIPHATIC AMIDES[a]

Compd.	Form[b]	Solvent	t-Butyl	NCH₃	CH₂	NH	
	K	$CDCl_3$[c]	1.17	2.82 (4.8)[d]	3.49	7.2	
	K	C_6H_6	0.93	2.55 (4.9)	3.27	*e*	
	K	C_5H_5N	1.11	2.87 (4.8)	3.72	*e*	
	E	C_6H_6	1.17	2.57 (5.0)	4.94	*e*	
	E	C_5H_5N	1.14	2.89 (4.8)	4.26	*e*	
Compd.		**Solvent**	**CH₃**	**NCH₂**	**CH₂**	**C_6H_5**	**NH**
		$CDCl_3$	2.21	4.42 (6.0)	3.37	7.28	7.3
		$CDCl_3$	2.18	4.38 (5.6)	3.33	7.26	7.3
		C_6H_6	1.73	4.27 (5.8)	2.95	*e*	*e*
		C_5H_5N	2.26	4.80 (6.0)	3.68	*e*	*e*
		$CDCl_3$	1.83	4.36 (6.4) 4.40 (5.7)[f]	4.36	7.27	5.2 9.5
		$CDCl_3$	1.80	4.34 (6.5)[h] 4.38 (5.7)[h]	4.38	7.27	5.3 9.5
		C_5H_5N	1.79	4.32 (6.5) 4.70 (6.1)	5.09	*e*	*e* *e*
		$CDCl_3$[g]	1.88	4.36 (6.3)	4.48		8.9

[a] In parts per million. [b] K, keto form; E, enol form. [c] No enol form detectable. [d] In cycles per second. [e] Not located. [f] Approximate. [g] Data from ref. 1. [h] ±0.3 c.p.s.

more, the ND deformation frequency appears at 1492 cm.$^{-1}$ (H–D = 1.06) confirming the assignments.

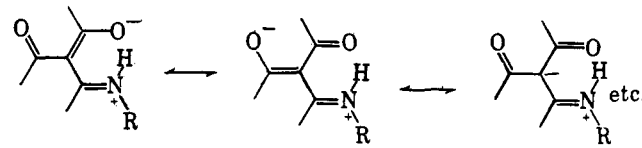
With 2-acetiminodimedone (IVb, R = H), the free carbonyl appears at 1648, the associated carbonyl appears at 1584, and the free NH deformation appears at 1642, while in N-methyl-2-acetiminodimedone (IVb, R = CH_3) the free carbonyl stretch appears at 1634 cm.$^{-1}$.

Discussion

The spectra of both N-benzylacetoacetamide (VII) and N-methyl-4,4-dimethyl-3-oxovaleramide (VIII) indicate that the tautomeric behavior of the 2-carbamoyldimedones is not a direct consequence of the amide function. On the contrary, the spectra show that the amide function inhibits enolization of the β-keto group as compared to an ester function. Therefore the enolic properties of the diketoamide group results from the second β-carbonyl group and the concomitant electronic interactions.

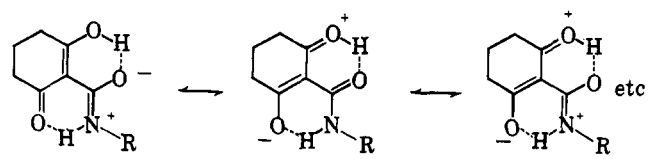
The properties of the Schiff bases derived from 2-acetyldimedone indicate that the electron-withdrawing power of the additional carbonyl is large and the strength of the hydrogen bond is increased by an amount corresponding to a chemical shift of nearly 3 p.p.m. Considering the indifference of the NH resonance to substitution at either the nitrogen or the carbonyl oxygen, the shift is noteworthy.

In terms of either resonance or simple Hückel molecular orbital theory,[1] the acetylacetone Schiff bases (*i.e.*, VI) are strongly polar with an appreciable negative charge at the middle carbon (position 3 in the acetylacetone series). The resonance forms described below illustrate how the electron-withdrawing power of the carbonyl accentuates the dipolar nature of the carbonylamine grouping. The infrared spectra show that even

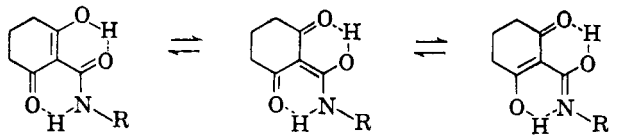


the stretching frequency of the nonchelated carbonyl of N-methyl-2-acetiminodimedone (IVb) is shifted to markedly lower frequencies (at 1634 cm.$^{-1}$) than that of a normal carbonyl (~1700 cm.$^{-1}$). This shift is a result of the electron delocalization in the system.

For 2-carbamoyldimedone, numerous resonance structures can be written for the system, among which are the following.



Another mode of describing the diketoamide interactions is the following limiting tautomeric (not resonance) forms.

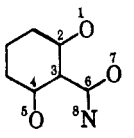


X XI XII

The two descriptions for the diketoamides are essentially equivalent. However the first set of structures overemphasizes the ionic nature of the interactions, while the second set overemphasizes the covalent nature of the tautomeric interaction.[19] Ordinarily the difference between tautomeric species and ionic resonance forms is large, but here the difference is due primarily to the position of the hydrogen.

Tautomer XI, the one favored by the crystal structure work,[2] contains three exocyclic double bonds, similar to the prevalent tautomer in 2-acetiminodimedone. The more symmetric imine structure of the Schiff base is formed in solution in preference to the asymmetric one, indicating some extra stability for this type of grouping.

To gain further insight into the diketoamides, molecular orbital calculations of the Hückel type were undertaken. For convenience, the positions were numbered as in (XIII) where the basic parameters for the various atoms were those discussed in ref. 1. The resonance integrals (β) were selected with the aid of the bond distances given by Donohue and his collaborators for aureomycin[2] (the effect of the dimethylamino group has not been included).



XIII

$\alpha_2 = \alpha_3 = \alpha_4 = \alpha_6 = \alpha_c$
$\alpha_8 = \alpha_c + 1.5\ \beta_c$
$\alpha_5 = \alpha_c + 1.2\ \beta_c$
$\beta_{4:5} = 1.2\ \beta_c$, $\beta_{3:4} = 0.9\ \beta_c$, $\beta_{6:8} = \beta_c$

Calculations were obtained for three variations in the diketoamide molecule. Using the conclusions obtained with aureomycin, the parameters were first adjusted to correspond to the hydroxy amine tautomer of the amide group XI. Atoms 1 and 5 are carbonyl oxygens, atom 7 is a hydroxyl, and 3:6 is a double bond; the following parameters were therefore used in addition to the basic ones given above: $\alpha_1 = \alpha_c + 1.2\ \beta_c$, $\beta_{1:2} = 1.2\ \beta_c$, $\beta_{3:6} = 0.9\ \beta_c$, $\alpha_7 = \alpha_2 + 2.5\ \beta_c$, $\beta_{6:7} = \beta_c$, and $\beta_{2:3} = \beta_c$.

By interchanging the coulomb integrals (α) for 1 and 7 as well as the resonance integrals (β) for bonds 1:2 and 6:7, the molecule is then converted into the normal carbonyl–amine structure for the amide X.

One more permutation was used for computing the third delocalization energy ("amide B"); the β for bonds 3:6 and 2:3 were interchanged in addition to the values used in the previous paragraph. This refinement allows for a possible shift in resonance interactions in XI $\leftrightharpoons$ X where 1:2 is a single bond and 2:3 is a double bond compared with aureomycin (1:2 is a double bond and 2:3 is a single bond).

The delocalization energies obtained are as follows: hydroxy amine (XI), $\Sigma\beta = 19.540$; "amide A" (X), $\Sigma\beta = 19.494$; "amide B" (X), $\Sigma\beta = 19.434$. Hence the difference in delocalization energy between the two tautomers is calculated to be about 0.05 β if no change in bond lengths (except the carbonyls) is involved. If there is an alteration in bond lengths ("amide B"), then the difference is about 0.11 β. Assuming $\beta = 20$ kcal. or less,[20] the difference in energy between tautomers is at most 2 kcal.[21] Small variations in hydrogen bond strength between tautomers could easily be as large as this calculated difference.

Although hydrogen bonding was not explicitly included in the Hückel calculations, the importance of the strong hydrogen bonds in these compounds should not be overlooked. Not only do they fix the geometry of the system, but the appreciable hydrogen bond energy is a stabilizing factor. In fact one could consider the possibility of a pseudo ring current about the perimeter of the diketoamide grouping.

None of the models consider the effect of the dimethylamino group at C-4 of the tetracycline system which, according to the pK_a values, increases the acidity of the enolic system.[3] However the interpretation of the tetracycline spectral data is complicated by both the limited solubility of these molecules in inert solvents and the number of exchangeable hydrogens present. The most conservative conclusion that can be drawn is that the diketoamide system is an unusual keto–enol tautomer—this is important in itself.

Acknowledgment.—We wish to thank Dr. Emily Pitcher Dudek for extensive editorial assistance and the Milton Fund of Harvard University for generous financial support.

(19) For a detailed discussion of the theoretical problems involved in a description of the hydrogen bond, see G. C. Pimental and A. L. McCellan, "The Hydrogen Bond," H. H. Freeman and Co., San Francisco, Calif., 1959, Chapter 8.

(20) A. Streitweiser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 9.

(21) It should be remembered that, owing to the many approximations and sources of error in the Hückel procedure, especially those involving several hetero atoms, these results should be considered just additional evidence.