was removed by dissolving the oil in Skellysolve B, seeding with amide and allowing to stand twenty-four hours. Evaporation of the filtered solution gave the desired base. These bases could be converted to the monohydrochlorides without further purification or distilled under vacuum to give pale yellow tinted oils. The latter are all quite stable to heat but on standing for several days at room temperature, where dialkyl is diethyl, the bases develop a beautiful lavender or purple color. In two instances (see Table II) the bases solidified and were recrystallized from Skellysolve B.

The monohydrochlorides were prepared by dissolving the free base in three volumes of isopropyl alcohol and adding slightly less than the equivalent amount of alcoholic hydrogen chloride. In order to induce crystallization, ether was added to turbidity, the inside of the flask scratched and the solution allowed to stand. The analytical samples were dried *in vacuo* at about 120°.

The monohydrochloride of 7-chloro-4-(3-dimethylamino-1-phenylpropyl)-quinoline could not be induced to crystallize. A dihydrochloride, m. p. 215–217°, was prepared but gave an unsatisfactory analysis.

Summary

The condensation of phenylacetonitrile with 4-chloro-, 4,5-dichloro- and 4,7-dichloroquinoline has been investigated under a variety of conditions. The resulting α-(4-quinolyl)-phenylacetonitriles were converted to the corresponding α-(4-quinolyl)-phenylacetamides and 4-benzylquinolines.

The preparation of the methyl α-(4-quinolyl)-phenylacetates from the corresponding nitriles and some basic esters and basic amides is reported.

The reaction of γ-dialkylamino-α-phenylbutyronitrile with 4-chloroquinolines is also described. The nitriles so formed were converted to the corresponding amides and 4-(3-dialkylamino-1-phenylpropyl)-quinolines.

RENSSELAER, NEW YORK RECEIVED APRIL 15, 1949

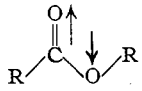
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA AND THE RESEARCH DIVISION OF CUTTER LABORATORIES]

The Dipole Moment of Methyl Benzylpenicillinate

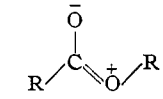
BY W. D. KUMLER, I. F. HALVERSTADT AND EDWARD L. ALPEN

Methyl benzylpenicillinate has been reported to have a dipole moment of approximately 8 from measurements in chloroform and anhydrous ethanol solutions.[1] It seems improbable that the molecule would have such a large moment if the commonly accepted structure of penicillin is correct. The large moment would mean that the individual moments were lined up in nearly the same direction, which is rather unlikely.

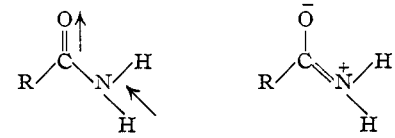
The group moments contributing to the over-all resultant moment are those of the ester (1.8), sulfide (1.6), amide (3.8)[2] and lactam (3.8 estimated). The moment of the lactam might be increased somewhat over an ordinary amide as a result of the ring formation, just as a lactone has a higher moment (4.1)[3] compared with an ester (1.8) but this increase in case of the lactam amide would be considerably less than in the case of the lactone. The ester is almost entirely in a form in which the ether dipole almost directly opposes the carbonyl dipole.



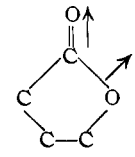
The molecule is held in this configuration by the contribution from the resonating form



which gives some double bond character to the carbonyl carbon–ether oxygen bond. The amides likewise are probably held in a similar configuration by resonance but here the moment of the amine portion (0.6–1.2) is not only smaller than that of the ether (1.3), but its resultant is not opposed to that of the carbonyl moment.



This effect is in part responsible for the dipole moment of amides being greater than that of a ketone (2.8), while that of an ester is considerably less. When an ester is bent around to form a lactone the moments are no longer directly opposed



but augment one another to some extent. However, when an amide is closed into a lactam there will not be nearly as much enhancement because there was originally not as much opposition to the

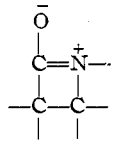
(1) O. S. R. D. Report Sh 4, 34 (1944) Shell Development Co. also the "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 407. This value was offered as an approximate value only. Although some workers interpreted this value as evidence for a zwitterion structure for penicillin, the Shell workers pointed out that although the value of 8 was intermediate between the moment of molecules without a separation of charge and the moment of zwitterion molecules, the fact that the molecule did not show a positive dielectric increment was evidence against its being a zwitterion.

(2) Kumler and Porter, THIS JOURNAL, **56**, 2549 (1934).

(3) Marsden and Sutton, *J. Chem. Soc.*, 1383 (1936).

carbonyl moment and the ring closure still leaves one of the N–H or N–C moments opposed to the carbonyl moment.

The lactam moment would also be reduced as a result of a decrease in the contribution of the resonating form



due to the additional strain in the four-membered ring caused by the double bond between carbon and nitrogen. There is evidence for this effect from the X-ray crystallographic studies. The carbonyl carbon–nitrogen distance in the lactam ring is given as 1.38 Å. and the carbonyl carbon–nitrogen distance in the amide as 1.33 Å.[4] The accuracy of the measurements is not sufficiently great to be certain of this difference but the reported distances are in the direction expected for less resonance in the lactam as compared with the amide. Not knowing the exact magnitude of either of these two effects we have assumed that the two cancel and the lactam has the same moment as the amide.

Taking the distances and angles given by the X-ray evidence for the solid, plus the above moments for the polar groups, we calculate the moment of methyl benzylpenicillin to be 5.2. The amide side-chain undoubtedly is not held in the same position in solution as it is in the solid. It would be expected to have some freedom of rotation, if not complete freedom of rotation, in solution. Assuming freedom of rotation for the amide side-chain the moment of the molecule is calculated to be 4.4. The expected moment of the compound is then somewhere between the two values.

The dipole moment of methyl benzylpenicillinate has been measured in dioxane solution at 25°. The method used in calculating the moment was that of Halverstadt and Kumler.[5] The ϵ_{12} values

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.01281\sqrt{(P_{2_0} - P_{E2_0})T}$$

were linear with respect to ω_2. The v_{12} values departed somewhat from linearity on the first series of measurements. Four additional solutions were then measured and the v_{12} values of these were linear with respect to ω_2. The values of ϵ_1 and v_1 were obtained by extrapolating the ϵ_{12} and v_{12} values to $\omega_2 = 0$. $P_{E_{2_0}}$ values were obtained from the refractive index of the more concentrated solutions.

(4) Chain (from work of Crowfoot, Bunn, Rogers-Low and Turner-Jones), *Endeavour*, **7**, 152 (1948).

(5) Halverstadt and Kumler, THIS JOURNAL, **64**, 2988 (1942).

MEASUREMENTS IN DIOXANE AT 25°, METHYL BENZYLPENICILLINATE

ω_2	ϵ_{12}	v_{12}
0.001951	2.2311	0.97353
.004392	2.2505	.97315
.006669	2.2690	.97277
.007647	2.2787	.97268
.008992	2.2892	.97259
.001262		.97291
.001875		.97382
.003981		.97333
.007306		.97268

ϵ_1 extrap.	v_1 extrap.	α	β	P_{2_0}	$P_{E_{2_0}}$	μ
2.2147	0.97418	8.28	−0.209	550.8	93.0	4.73

The observed dipole moment of methyl benzylpenicillinate is 4.73 with an estimated accuracy of ±0.02. The value is within the range of the moment calculated using the accepted structure of benzylpenicillin. This value of the dipole moment is further confirmatory evidence for the correctness of the generally accepted structure of penicillin and removes any support which the higher reported dipole moment value of 8 gave to the previously proposed zwitterion-incipient azlactone structure for penicillin.[6]

Materials

Dioxane.—Dioxane was purified as before.[7]

Methyl Benzylpenicillinate.—Fifteen grams of potassium benzylpenicillin assaying 1577 units per mg. was treated by a modification of the procedure given in the Merck O.S.R.D. Report M-15b p. 1, and also in the "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 93. The ether solution of the free acid was dried by freezing out the ice at −70° and filtering. The solution was treated with a slight excess of diazomethane. Esterification was complete in fifteen minutes. The solution was concentrated *in vacuo* to an oily residue weighing 30 g. which was diluted with 70 g. of carbon tetrachloride and seeded with crystals by courtesy of D. S. Melstrom of Shell Development Co. After standing overnight the crystals were filtered off and dried; yield 10 g. Additional material was recovered to make a total of 11.26 g. This material was crystallized once from ether and once from carbon tetrachloride to yield 9.55 g. which softened at 94–95° and melted at 96–97° at 3° per min.

Summary

The dipole moment of methyl benzylpenicillinate was measured in dioxane and found to have a value of 4.73. This observed value is consistent with the calculated value using the usual group moments and the accepted structure of penicillin. Any support which the previously reported moment of 8 gave to the once proposed zwitterion-incipient azlactone structure for penicillin is thus removed.

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(6) Committee on Medical Research O. S. R. D., Washington, and Medical Research Council, London, *Science*, **102**, 627 (1945).

(7) Kumler and Halverstadt, THIS JOURNAL, **64**, 1941 (1942).