Conversion of A to C.—One gram of A was dissolved in 10 ml. of acetic acid, and 1 ml. of concentrated sulfuric acid was added at room temperature. The solution immediately turned dark green. The temperature was prevented from rising by cooling in an ice-bath. After five minutes of swirling, the mixture was poured into ice-water from which an oil separated which solidified after a few minutes. Four recrystallizations from absolute ethanol and two from 95% ethanol gave a small amount of light yellow crystals, m.p. 258–262° with darkening.

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.48; N, 8.00; mol. wt., 350. Found: C, 75.17; H, 7.50; N, 8.18; mol. wt. (cryoscopic in camphor), 306.

Hydrogenation of A.—A solution of 2 g. of A in 100 ml. of 95% ethanol with 0.2 g. of Adams catalyst was hydrogenated at about three atmospheres pressure at 55° for 4 hr. After removal of the catalyst, the yellow solution was concentrated and cooled to give 0.8 g. of white solid, m.p. 274–278°, and a second crop of 0.3 g., m.p. 265–270°. Combination and recrystallization raised the melting point to 276–284°. An analytical sample melted at 281–284°.

Anal. Calcd. for $C_{22}H_{28}O_2N_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.94, 75.09; H, 7.78, 7.92; N, 7.65, 7.79.

Hydrogenation of B.—Employing the conditions used for A, 430 mg. of B gave 320 mg. of white crystals which after one recrystallization from 95% ethanol melted at 280–284°. The infrared spectrum of this product was identical with that of the hydrogenation product of A; mixed m.p. 280–283°.

Conversion of H_2A to D.—A mixture of 400 mg. of H_2A and 2.7 ml. of 75% sulfuric acid was heated at approximately 100° for 30 minutes. The solution turned dark red during this period. A solid separated when the mixture was poured into ice-water. Two recrystallizations from 95% ethanol gave 140 mg. of white solid, m.p. 240–243°. An analytical sample melted at 241–243°.

Anal. Calcd. for $C_{22}H_{22}O_2N_2$: C, 74.97; H, 8.01; N, 7.95; mol. wt., 352. Found: C, 74.79, 75.03; H, 7.79, 7.89; N, 7.9, 8.25; mol. wt. (cryoscopic in camphor), 310, 303.

Ozonolysis of B.—A solution of 290 mg. of B in about 100 ml. of ethyl acetate was treated with ozone for 30 minutes after which time the absorption of ozone ceased. The solution was evaporated to dryness under reduced pressure to give a yellow oil. The oil was treated with 75 ml. of 10% sulfuric acid, and about 50 ml. of the mixture was collected by distillation. To the distillate was added a solution of 125 mg. of methone in a few cc. of 95% ethanol followed by a few drops of piperidine. After the solution had been allowed to stand, about 140 mg. of solid separated which after one recrystallization from dilute ethanol melted at 187–188°; mixed m.p. with an authentic sample of the dimethone derivative of formaldehyde showed no depression.

Ultraviolet Spectra.—All the spectra were determined in 95% ethanol.

	λmax, mμ	log ε	λmin, mμ	log ε
A	236	4.42	285	3.68
	338	3.84	405	2.95
	420	2.97		
B	255	4.41	225	4.20
	310	3.80	300	3.78
C	255	4.43	223	4.04
	315	3.80	300	3.75
D	258	4.40	230	3.88
	307	3.94	280	3.78
H_2A	258	4.40	230	3.88
	305	3.94	285	3.82

Major Infrared Absorption Bands.—The potassium bromide pellet technique was employed with a Baird double beam instrument, unless otherwise noted. Bands in the 5–13 μ region are given (in microns). A: 5.96, 6.01 (shoulder at 6.10), 6.23, 6.39, 6.96, 7.13, 7.77, 9.49, 9.82, 11.34, 12.61; B: 5.97 (shoulder at 5.92), 6.10, 6.23, 6.42, 6.92, 7.18, 7.92, 8.10, 8.67, 9.61, 9.88, 11.31, 11.47, 12.06; C (in Nujol): 5.97, 6.08, 6.24, 6.42, 8.07, 8.58, 10.25; D: 6.01 (shoulder at 5.98), 6.27, 6.43, 6.92, 7.18, 7.77, 8.10, 8.59, 8.92; H_2A: 6.00, 6.22, 6.41, 6.97, 7.17, 7.82, 8.60, 9.22, 9.82, 10.66, 11.17; 1,2,5-trimethyl-3,4-diacetylpyrrole (III): 6.08 (shoulder at 6.03), 6.52, 7.07, 7.23, 7.78, 8.59, 10.27, 10.48.

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Analogs of Tetracycline. I. Preparation of 1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl) Propane-1,3-dione and 1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene

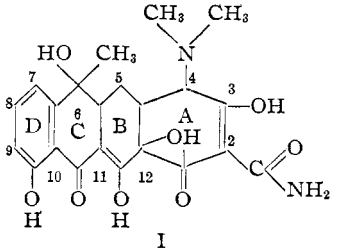
BY EDWARD E. SMISSMAN AND R. BRUCE GABBARD

RECEIVED DECEMBER 3, 1956

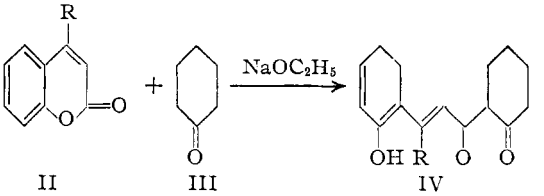
A method for the preparation of A and D ring analogs of tetracycline is discussed. This method, the reaction of coumarins with cyclohexanone, gave rise to 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene and 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione. A preparation for ethyl-2,2-ethylenedioxycyclohexane carboxylate is given.

We have initiated a study of A-D ring analogs of the tetracycline molecule, I. Our interest was directed toward the preparation of a molecule having the same four oxygen functions as are present in position 1, 10, 11 and 12 of the parent compound.

We decided to investigate the possible formation of our desired system by the reaction of the sodio derivative of cyclohexanone, III, and the properly substituted coumarin, II. The reaction between coumarin and sodio-organic compounds other than sodium alkoxides[1] has not been reported.



I

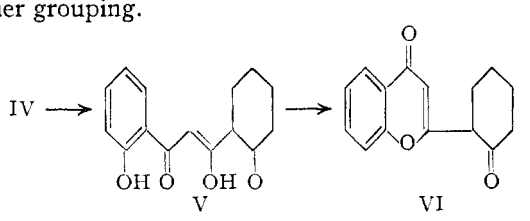


II III IV

(A) R = H–
(B) R = $-OC_2H_5$
(C) R = –OH

(1) K. Fries and W. Klostermann, *Ann.*, **362**, 1 (1908).

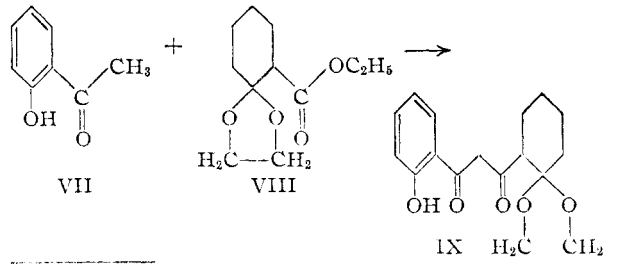
The initial reaction in the series was between coumarin (IIA) and cyclohexanone (III). This reaction was carried out in the presence of sodium ethoxide and gave a 19% yield of 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene (IVA). The reaction was then extended to the use of 4-hydroxycoumarin (IIC), but insolubility of the sodium salt in the reaction solvent prevented it from condensing with the cyclohexanone anion. Logically, we protected the enolic hydroxyl group as the enol ether, and using 4-ethoxycoumarin (IIB), in the reaction with cyclohexanone we obtained 1-(2-hydroxyphenyl)-1-ethoxy-3-keto-3-(2-ketocyclohexyl)-1-propene (IVB). We acidified this product during the workup and the enol ether, IVB, produced 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione (V) in 6% yield. After standing in a 10% aqueous hydrochloric acid solution, V formed a compound VI, which was soluble in 10% sodium hydroxide but not in saturated sodium bicarbonate solution. This compound gave a deep-red color with sulfuric acid. We postulated a flavone structure, and the spectral and analytical data indicated the compound VI to be 2-(2-ketocyclohexyl)-flavone. In the infrared spectrum there was no indication of a hydroxyl group in the 3 μ region, but a medium band at 8.15 μ was present. This band at 8.15 μ has been reported[2] to be indicative of the C=C—O⁻R ether grouping.



V VI

Variations in temperature and time failed to increase the poor yield of V. We attempted to use sodamide, triphenylmethylsodium and sodium dispersion as catalysts but to no avail.

A second method of preparing the desired compound V was tried. The condensation of 2-hydroxyacetophenone (VII) with ethyl 2,2-ethylenedioxycyclohexanone carboxylate (VIII) would give a product IX, which on acidification should lead to V. The synthesis of ethyl 2,2-ethylenedioxycyclohexanecarboxylate had not been reported, and we were successful in preparing this compound. However, the condensation, using sodium ethoxide as a catalyst, did not take place in amounts great enough to allow us to isolate the desired compound. We did not attempt the condensation using other catalysts.



VII VIII IX

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

Experimental

1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene (IVA).—A solution of 6 ml. of absolute ethanol in 100 ml. of dry toluene was placed in a 500-ml. three-necked flask. In the presence of a nitrogen blanket, dispersed sodium[3] was added (CARE!) until the toluene solution turned gray (excess sodium). One to two ml. of absolute ethanol was added to discharge the gray color of the suspension. A solution of 9.8 g. (0.1 mole) of cyclohexanone and 14.6 g. (0.1 mole) of coumarin in 100 ml. of dry toluene was added to the contents of the flask. The stirred suspension, initially yellowish-white in color, immediately changed to dark brown and considerable heat was evolved. The solution was stirred for 4 hr. The mixture was shaken with 200 ml. of water and the non-aqueous layer discarded. The aqueous layer was acidified to *p*H 2 with concd. HCl. The milky suspension was extracted twice with ether and on evaporation the ether extracts gave a dark brown viscous oil. This oil was dissolved in 50 ml. of ethanol and a saturated solution of cupric acetate was added until precipitation was complete. The greenish precipitate of the cupric complex was collected and placed in a separatory funnel containing 100 ml. of H_2O and 50 ml. of ether; 25 ml. of concd. HCl was added. The funnel was shaken occasionally to facilitate the decomposition of the copper complex. The ether layer on evaporation gave a brown viscous oil. The oil was dissolved in saturated sodium bicarbonate solution. On acidification, a solid product, 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene monohydrate, separated. It required three to four repetitions of the procedure of dissolving the original material in sodium bicarbonate and acidifying to convert all of the material to the tan monohydrate; yield 5 g. (19%), m.p. 127° dec.

Anal. Calcd. for $C_{15}H_{16}O_3 \cdot H_2O$: C, 68.75; H, 6.88; neut. equiv., 262. Found: C, 68.80, 69.04; H, 6.49, 6.94; neut. equiv., 259.

4-Ethoxycoumarin (IIB).—The method of Anschütz[4] was followed; 4-hydroxycoumarin was treated with equal molar quantity of sodium ethoxide and then allowed to react with ethyl iodide. From 48.6 g. (0.3 mole) of 4-hydroxycoumarin, 25 g. (44%) of colorless prisms of 4-ethoxycoumarin was obtained, m.p. 136–138° (lit. 136°).

1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione (V).—A solution of 3 ml. of absolute ethanol in 100 ml. of dry xylene was placed in a 500-ml. three-necked flask. The procedure was identical to that described for the preparation of IVA using a solution of 9.5 (0.05 mole) of 4-ethoxycoumarin and 5.3 g. (0.5 mole) of cyclohexanone in 100 ml. of dry xylene. The ether extract of the copper complex decomposition gave 0.80 g. of a brownish yellow oil. One hundred mg. of the compound was treated with a solution of 2,4-dinitrophenylhydrazine as described by Shriner and Fuson.[5] Orange needles were obtained from chloroform–alcohol recrystallization, m.p. 206–208°.

Anal. Calcd. for $C_{27}H_{24}N_8O_{10}$: C, 52.26; H, 3.87. Found: C, 52.20; H, 3.89.

2-(2-Ketocyclohexyl)-flavone (VI).—Two hundred milligrams of 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione was allowed to stand in 50 ml. of 10% HCl. The oil solidified to a yellow amorphous mass within two days. After recrystallization from acetic acid–water, 150 mg. (80%) of a yellowish amorphous powder, m.p. 102–104°, was obtained.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.06; H, 6.26. Found: C, 73.72; H, 6.40.

Ethyl 2,2-Ethylenedioxycyclohexanecarboxylate (VIII).—A homogenous, clear solution was prepared by mixing 50 ml. of thiophene-free benzene, 50 ml. of ethylene glycol and 100 ml. of 1,4-dioxane. To 125 ml. of this solution was added 17.6 g. (10.1 moles) of ethyl 2-cyclohexanone carboxylate and 20 mg. of *p*-toluenesulfonic acid monohydrate. The flask containing this mixture was connected to a mois-

(3) Sodium dispersion, 50% sodium by weight, in xylene with 1% Armeen 12 and 1% oleic acid. Supplied by U. S. Industrial Chemicals Company.

(4) R. Anschütz, *Ann.*, **367**, 169 (1909).

(5) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

ture trap and the mixture refluxed until water no longer separated in the trap. The time required was 18 hr. The benzene and dioxane were distilled and the residue was treated with 100 ml. of 1% aqueous sodium hydroxide and the solution extracted twice with 50-ml. portions of ether. The ether was evaporated leaving a liquid which was distilled to give 13 g. (60%) of a colorless material, b.p. 259–261° (atmosphere); 170–174° (14 mm.); $n^{25}D$ 1.4640.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.12; H, 8.24.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOJINDO & CO., LTD.]

Polyazobenzenes. III. Infrared Absorption Spectra of Some Polyazobenzenes

BY KEIHEI UENO

RECEIVED DECEMBER 26, 1956

Infrared absorption frequencies from 4000 to 650 cm.$^{-1}$ are reported for seventeen polyazobenzenes including their nitro, amino and hydroxy derivatives. Frequencies are assigned in most cases to bond or group vibrations, and the results are discussed in relation to their structure. Tentative assignment was made for the N=N bond at 1400 and 1455 cm.$^{-1}$.

Introduction

Le Fèvre and his co-workers[1] have investigated some 43 aromatic diazonium and azo compounds and found common absorption bands at around 1406 and 1577 cm.$^{-1}$. However, their result was not conclusive, and more fundamental information on the infrared absorption spectra of aromatic azo compounds is badly needed from both theoretical and practical standpoints. It is the purpose of this investigation to analyze the infrared absorption spectra of polyazobenzenes and their nitro, amino and hydroxy derivatives, as well as polyazostilbenes, which can be considered as model structures of commonly used azo dye molecules. The result of such a study should be of importance in connection with the infrared analysis of azo dyes of more complicated structures.

Experimental

Compounds chosen for this investigation are identical with those which were previously synthesized for our ultraviolet absorption study, and details of their syntheses have been described.[2] Since it was almost impossible to prepare solid samples of stereochemically pure isomers for most of the compounds, the infrared absorption measurements were carried out on samples neglecting their stereochemical purity, although they are believed to consist mainly of *trans* isomers.

A Perkin–Elmer model 21 double beam spectrophotometer equipped with sodium chloride optics was used for the measurements, and samples were run both as Nujol mulls and as potassium bromide disks. For most of the samples, the Nujol run and the potassium bromide disk run gave almost the same absorption spectra; however, better resolution was observed in the latter technique, and additional bands were found in the region where the Nujol bands overlap.[3]

Result and Discussion

The significant absorption bands observed below 1650 cm.$^{-1}$ are presented in Table II, along with the assignments to the group vibrations wherever possible.

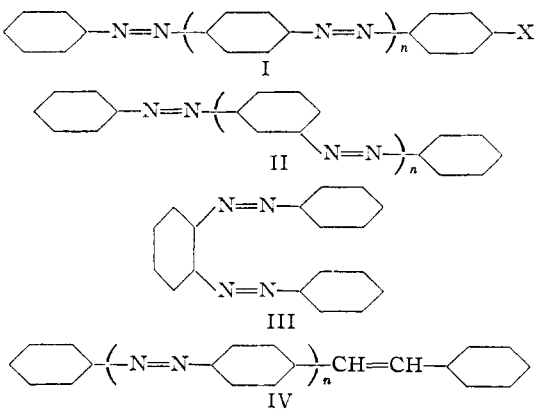
(1) R. J. W. Le Fèvre, M. F. O'Dwyer and R. L. Werner, *Australian J. Chem.*, **6**, 341 (1953).

(2) K. Ueno, THIS JOURNAL, **74**, 4508 (1952); K. Ueno and S. Akiyoshi, *ibid.*, **76**, 3667 (1954).

(3) Infrared absorption spectra of some of these compounds have been published in the Sadtler Infrared Catalog: however, their spectra were taken by the Baird double beam spectrophotometer of linear wave length on Nujol mull samples. Since our spectra were recorded in linear wave number with potassium bromide technique, more precise investigation was possible, especially in the 3000 and 1600 cm.$^{-1}$ regions.

TABLE I

LIST OF THE COMPOUNDS INVESTIGATED



Compound no.	Name of compound	Structural description: Type	*n*	X
1	Azobenzene	I	0	H
2	4-Phenylazo-azobenzene	I	1	H
3	4,4'-Bis-(phenylazo)-azobenzene	I	2	H
4	4-Hydroxy-azobenzene	I	0	OH
5	4-Hydroxy-4'-phenylazo-azobenzene	I	1	OH
6	4-Phenylazo-4'-(*p*-hydroxyphenylazo)-azobenzene	I	2	OH
7	4-Aminoazobenzene	I	0	NH_2
8	4-Phenylazo-4'-aminoazobenzene	I	1	NH_2
9	4-Phenylazo-4'-(*p*-aminophenylazo)-azobenzene	I	2	NH_2
10	4-Nitroazobenzene	I	0	NO_2
11	4-Phenylazo-4'-nitroazobenzene	I	1	NO_2
12	4-Phenylazo-4'-(*p*-nitrophenylazo)-azobenzene	I	2	NO_2
13	3-Phenylazo-azobenzene	II	1	
14	3,3'-Bis-(phenylazo)-azobenzene	II	2	
15	2-Phenylazo-azobenzene	III		
16	4-Styryl-azobenzene	IV	1	
17	4-Styryl-4'-phenylazo-azobenzene	IV	2	

In general, the absorption patterns of each set of polyazobenzenes are found to be almost identical but become broader and more diffuse when the number of azo linkages increases. The same tendency was reported for the amino acids and the corresponding polypeptides.[4]

(4) E. Ellenbogen, THIS JOURNAL, **78**, 366 (1956).