No oxygen uptake was observed when ethyl acetate served as the solvent. The solution was filtered from the catalyst and brought to *p*H 9 by adding 4 *N* KOH at 0°. A negligible amount of basic material separated and was discarded. Concentrated alkali was added at 0°. The resulting base was extracted into ether, in which it was not very soluble. Some of the base crystallized at the interface and was collected by filtration. The residue from the ether extract as well as the crystals from the interface were recrystallized from acetone. Short colorless needles were obtained, m.p. 183° (yellow melt, evolution of gas). The compound turned starch-iodide paper blue.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 73.08; H, 8.04; N, 9.24.

Infrared Spectrum ($CHCl_3$).—2.84 μ (weak, broad band); 3.16 (shallow, broad band); 3.98 (shoulder); 4.35vw; 6.20vw; 6.36s; 6.85vs; 7.26w; 7.9w; 7.52w; 8.76m; 8.90m; 9.88w; 10.40m; 11.55m. When VI was left in chloroform solution for two days, a strong new band at 3.17 and a weak band at 5.74 μ developed.

Microtitration.—A 0.01 *M* solution in 50% water–alcohol showed 12.3 *p*H units at 20°. The microtitration gave values of *pK* 12.13 and 9.65. In 80% methyl Cellosolve (starting *p*H 12.28) *pK* inflection points at 11.0 and 5.5 were observed on titration with 0.01 *N* HCl. The neutralization equivalent was within 2% of theory.

Hydrochloride.—The addition of HCl gas to a chloroform solution of the hydroperoxide yielded tufts of needles, sintering and partial melting 180–185°, subliming in needles at 210°, melting again at 275–278°. Found: C, 61.76; H, 7.49; N, 7.33. (Calcd. for $C_{19}H_{26}N_2O_2 \cdot HCl \cdot H_2O$: C, 61.95; H, 7.93; N, 7.60.)

Conversion of the Hydroperoxide VI into the Base V. A. By Sublimation *in Vacuo*.—A small sample of the hydroperoxide was warmed in a molecular still to 180° (0.001 mm.). The crystalline material, washed down from the "cold finger," crystallized from ether in prisms, m.p. 188°, undepressed on admixture with base V, m.p. 188. The picrate was prepared (m.p. 172°) and identified with the picrate of base V by mixed m.p. and analysis.

B. By Rearrangement of the Hydroperoxide in Chloroform.—A solution of 0.5 g. of hydroperoxide VI in 40 cc. of chloroform, containing a few drops of a 4 *N* solution of HCl in ether, was refluxed until the test with potassium iodide–starch paper was negative. This took 50 minutes. From the chloroform solution there crystallized on cooling clear colorless prisms of a hydrochloride, m.p. 285–287° (sublimation 200–240°). Found: C, 65.68; H, 8.71; N, 8.12; Cl, 11.51. Calcd. for $C_{19}H_{26}N_2O \cdot HCl \cdot {}^3/_4H_2O$: C, 65.52; H, 8.25; N, 8.04; Cl, 10.6.

The infrared spectrum of this hydrochloride was practically identical with that of base V (2.73; 3.14; 4.06w; 6.18vs).

The mother liquors were fractionated on a column of 20 g. of alumina using 10-cc. portions of chloroform for elution. Fractions 4 and 5 (24 mg.) were ether-soluble, gave an ether-insoluble hydrochloride and showed the following bands in the infrared; 3.05 (broad); 5.98vs; 6.21s; 5.97vs; 6.01vs; 6.21s; 6.37m; 6.73vs. The ultraviolet spectrum showed only very weak absorption at 310 mμ where *o*-acylaminophenones absorb. A later fraction 13 (5 mg.) showed the following infrared bands: 3.10 (broad); 5.73s; 6.18s; 6.34s.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

The Self-condensation of 1,2,5-Trimethyl-3,4-diacetylpyrrole[1]

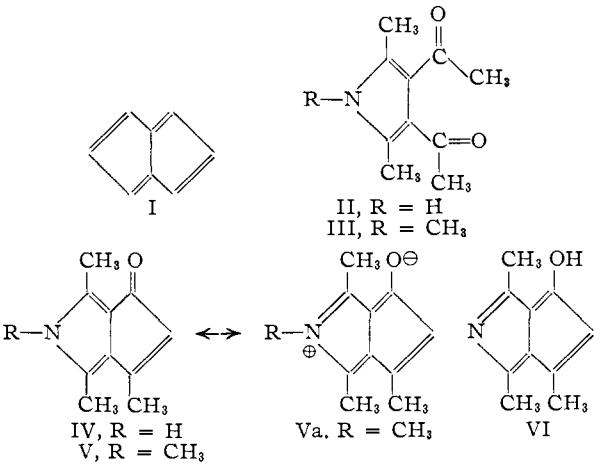
BY D. BRUCE BRIGHT[2]

RECEIVED NOVEMBER 24, 1956

1,2,5-Trimethyl-3,4-diacetylpyrrole condenses in the presence of sodium isopropoxide to give two products to which structures VIII and IX have been assigned as the most probable. The formation and reactions of these products are discussed in connection with the possible aromaticity of the pentalene system, and it is concluded that no significant resonance stability of the pentalene type is present in an apparently favorable case.

With the exception of a few dibenzo-derivatives,[3] previous attempted syntheses of the pentalene system[4] (I) have been unsuccessful. The present work is concerned with the attempted synthesis of an azapentalene. This plan was chosen because the nitrogen analog would be expected to have about the same resonance energy as the carbocycle and the fact that suitable starting materials were readily available. The scheme adopted was to start with a suitably substituted pyrrole nucleus and to form the second five-membered ring by a cyclization reaction. The attempted cyclization of 2,5-dimethyl-3,4-diacetylpyrrole (II) with several basic catalysts was unsuccessful, presumably because of the initial formation of the salt from the acidic N–H group rather than an active methyl group.

Such a cyclization would have resulted in the formation of the bicyclic product IV or its enol VI, a hydroxytrimethylazapentalene. To test the feasibility of this type of cyclization, 1,2,5-trimethyl-3,4-diacetylpyrrole (III), in which the N–H group is substituted, was subjected to treatment with sodium isopropoxide in isopropyl alcohol. The expected product (V) was not obtained but instead two compounds (A and B) whose analyses



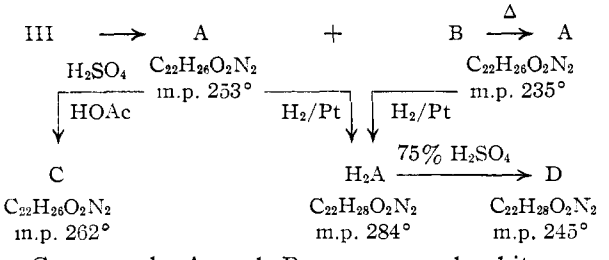
(1) Presented at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) Department of Chemistry, Purdue University, Lafayette, Indiana.

(3) C. T. Blood and R. P. Linstead, *J. Chem. Soc.*, 2263 (1952).

(4) For a review see J. W. Cook, "Progress in Organic Chemistry," Vol. III, Butterworths Publications, Ltd., London, 1955, p. 68.

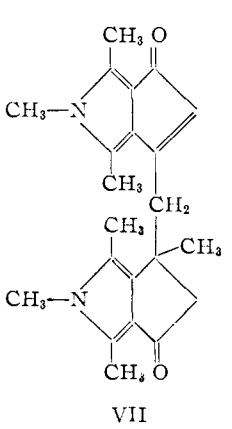
and molecular weights indicated them to be dimers of V. This reaction and some of the subsequent reactions of these two products are shown



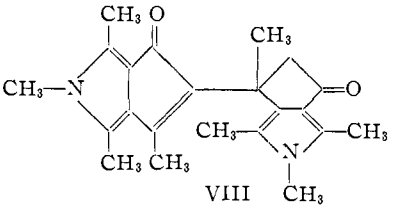
Compounds A and B, orange and white, respectively, could be separated by fractional recrystallization. From a rough separation of A and B from the reaction mixture, it is estimated that A is formed in about 45% yield and B in about 15%. Compound B when heated at its melting point underwent considerable decomposition but was in part converted to its isomer, A. It was observed that A is very sensitive to acids, a fact which hindered the formation of carbonyl derivatives. From the treatment of A with acidic solutions, a light yellow compound (C), isomeric with A and B, was formed in low yield in addition to considerable tar. The hydrogenation of both A and B proceeded readily with platinum oxide catalyst to give the same dihydro-derivative (H_2A). In view of this fact and the marked difference in the ultraviolet spectra of the compounds (see Experimental), it can be concluded that A and B differ only in the position of a double bond. Since compound C is difficult to obtain in a pure state, it proved unfeasible to obtain its hydrogenation product. However, the striking similarity in the ultraviolet spectra of B and C suggests that they have closely related or identical electronic systems. The infrared spectra of both A and B and their derivatives indicated in the above chart all exhibit carbonyl absorption at 5.96–6.01 μ and no absorption in the N–H or O–H regions (see Experimental).

The evidence is fairly conclusive that compound A does not have an acetyl group. The compound is recovered unchanged when treated with sodium hypoiodite while an acetylpyrrole would be expected to undergo the iodoform reaction or suffer replacement of the acetyl group.[5] Furthermore, treatment of H_2A with 75% sulfuric acid, a method for removing acyl and ester groups from a pyrrole nucleus,[6] results only in the isomerization of H_2A to D. The ultraviolet spectra of H_2A and D are essentially identical, suggesting that the conversion may involve only a stereochemical change. The product obtained from the lithium aluminum hydride reduction of A proved to be too unstable to be isolated in a pure state. The attempted oxidation of A with potassium permanganate also was unsuccessful.

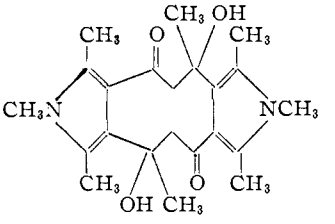
Of the possible structures for A consistent with these data and which might logically be formed from III, the most likely appear to be VII and VIII. Their formation can be visualized as an initial cyclization to form V, followed by a Michael reaction with another molecule of V or the intermediate hydroxyketone. An initial intermolecular condensation to form a compound such as X, which might conceivably react further undergoing cyclization and dehydration to form a product with only one double bond outside of the pyrrole rings, appears unlikely since a preparation of A using the dilution technique gave essentially the same results as the normal procedure. Furthermore, the presence of methyl groups in the 1-, 2- and 5-positions of the starting pyrrole (III) would be expected to favor an initial intramolecular condensation.



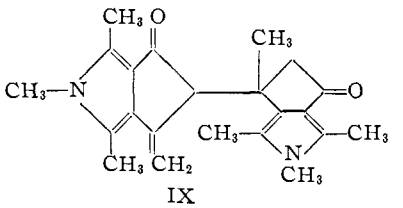
VII



VIII



X



IX

The experimental facts can be accounted for more readily on the basis of structure VIII rather than VII. Thus if compound A is VIII, B must be IX, since no other position of the double bond is possible. Catalytic hydrogenation of both these structures would be expected to give the same dihydro-derivative with the adjacent substituents on the five-membered ring in a *cis* configuration. The observed isomerization with strong acid may involve conversion to the more stable *trans* isomer. It would be predicted that the dimerization of V *via* a Michael reaction would give VIII (through the intermediate IX) rather than VII, by analogy to the fact that the alkylation of γ-extended enolate ions takes place preferentially in the α-position.[7]

A definite decision between the possible structures VII and VIII for A can be made on the basis of whether or not a methylene group is present in

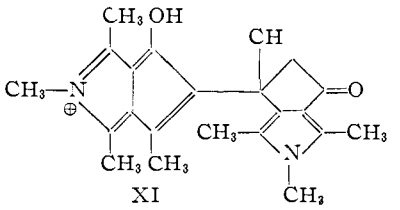
(5) See H. Fischer and H. Orth, "Die Chemie Des Pyrrols," Vol. 1, Akademische Verlagsgesellschaft G.m.b.H., Leipzig, 1934, p. 183.

(6) H. Fischer and E. Bartholomäus, *Z. physiol. Chem.*, **80**, 6 (1912).

(7) E. J. Corey, H. J. Burke and W. A. Remers, THIS JOURNAL, **78**, 180 (1956).

its double bond isomer B. This group would be present in B (IX) if A is correctly formulated as VIII but absent if A is VII. A clear-cut distinction between these two possibilities could not be made by an examination of the infrared spectrum of B. Although the spectrum shows a strong band characteristic of a methylene group[8] (11.47 μ), it is also consistent with a structure containing a trisubstituted ethylene group (the group which would be present in B if A were VII) having an absorption band at 12.06 μ.[8a] However, the presence of a methylene group in B was confirmed readily by ozonolysis of the material, from which formaldehyde was obtained, isolated as its demethone derivative. Thus VII is eliminated as a possibility leaving VIII as the most probable structure for A and consequently IX as B.[9]

If these structural assignments are correct, it appears that no great stability is conferred to A by contributions from resonance structures of the type Va. This is indicated by the fact that significant quantities of IX (B) can be isolated, since it would be expected to isomerize to VIII under the reaction conditions if the isomerization were energetically favorable. Also, the fact that V apparently dimerizes readily indicates no great stability of the system. Especially surprising is the extreme sensitivity of A to acids, as it might be supposed that the attachment of a proton to the carbonyl oxygen of the more unsaturated bicyclic system in VIII



XI

would produce a relatively stable azapentalene cation (XI). Actually a small quantity of the isomeric material C is all that could be isolated. Thus it is apparent that the ion XI is unstable relative to some competing process—presumably a carbonium ion rearrangement. In contrast to this behavior the stability of the more saturated compound D to strong acids should be noted. Thus it appears that these results offer no evidence for the formation of a resonance-stabilized system of the pentalene type in a case which otherwise appears favorable.

(8) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, pp. 31–46. (b) D. E. Applequist and J. D. Roberts, THIS JOURNAL, **78**, 4012 (1956).

(9) The referee has pointed out an apparent inconsistency in the ultraviolet spectra of the products with the proposed structures: namely, that the spectrum of A should exhibit absorption bands at approximately 255 and 310 mμ as found in the spectra of B, C, H_2A and D, since the proposed formulation contains one β-acylpyrrole portion. Two such isolated portions would be present in H_2A and D as formulated. Taking into account the factor of 1/2, the contribution of one acylpyrrole system to the log ϵ values for A is calculated to be 4.11 and 3.61 at 258 and 305 mμ, respectively (using the spectrum of H_2A as a basis). The actual spectrum of A is characterized by lack of fine structure, and the log ϵ values found at these wave lengths are 4.26 and 3.78, respectively. Thus, the spectrum of A is consistent with structure VIII.

Experimental[10]

Attempted Cyclization of 2,5-Dimethyl-3,4-diacetylpyrrole.—One gram of 2,5-dimethyl-3,4-diacetylpyrrole[11] was refluxed in 20 ml. of 10% sodium hydroxide for 1 hr. The yellow solution was allowed to cool, and 0.8 g. of a slightly yellow solid crystallized, m.p. 177–180°; mixed m.p. with II showed no depression. The reaction also was attempted with sodium *t*-butoxide in *t*-butyl alcohol, sodium hydride in ether and sodium hydride in toluene. In each case decomposition of the sodium salt with water gave starting material.

1,2,5-Trimethyl-3,4-diacetylpyrrole.—A procedure similar to that used for 2,5-dimethyl-3,4-diacetylpyrrole[11] was employed. To a mixture of 64 g. of 25% aqueous methylamine and 200 ml. of acetic acid was added 50 g. of *sym*-tetraacetylethane, and the mixture was heated at its boiling point for ten minutes. The red-black solution was allowed to cool and was then basified with an excess of saturated sodium carbonate solution. The solid was removed by filtration and recrystallized from a water–ethanol mixture; yield 29.5 g. (60%), m.p. 138–140°. A sample purified for analysis by four recrystallizations from dilute ethanol melted at 143–144°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.36; H, 7.83; N, 7.25. Found: C, 68.68; H, 7.78; N, 7.18.

Reaction of 1,2,5-Trimethyl-3,4-diacetylpyrrole with Sodium Isopropoxide.—A solution of sodium isopropoxide in isopropyl alcohol was prepared by dissolution of 8 g. of sodium hydride in 800 ml. of isopropyl alcohol. To this solution was added 29.5 g. of 1,2,5-trimethyl-3,4-diacetylpyrrole, and the solution was refluxed for 4 hr. The dark red solution was concentrated at water-pump pressure and diluted with water to precipitate an orange solid. After recrystallization from 95% ethanol, about 11 g. (41%) of a light orange product (A) was obtained, m.p. 247–252° with considerable darkening. A sample was recrystallized four times from 95% ethanol; m.p. 251–253°.

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.48; N, 8.00; mol. wt., 350. Found: C, 75.60; H, 7.49; N, 7.91; mol. wt. (cryoscopic in camphor), 306. (ebullioscopic in chloroform), 362.

From a collection of residues from the recrystallization of different fractions of A, recrystallization from 95% ethanol resulted in the separation of two types of crystals: the small orange crystals (A) described above and also some large light yellow crystals with hexagonal faces. Mechanical separation and repeated recrystallization of the yellow crystals from 95% ethanol with treatment with decolorizing charcoal finally gave a white crystalline product (B), m.p. 231–235°.

Anal. Found: C, 74.98, 74.87; H, 7.68, 7.57; N, 7.72, 7.80.

In another experiment a solution of 10 g. of III in 50 ml. of benzene and 250 ml. of isopropyl alcohol was added dropwise to a refluxing stirred solution of the catalyst over a period of 24 hr. The reaction mixture was neutralized with concentrated hydrochloric acid, the sodium chloride removed and the black solution evaporated to dryness *in vacuo*. A rough separation of the products was effected by extraction of B with small portions of 95% ethanol, crystallization of the extract, concentration and further recrystallization. By this procedure a portion of 6.5 g. of the residue gave 3 g. (46%) of crude A, 1.2 g. (18%) of crude B and a tar-like black material (36%) from which no crystalline substance could be isolated. Compound A did not give a positive 2,4-dinitrophenylhydrazine test but apparently underwent the change caused by the acidic solution (see below). Compound A was recovered unchanged when subjected to the iodoform test.

Conversion of B to A.—Two hundred milligrams of B was heated in a test-tube at approximately 230° for five minutes. During this time the material melted and turned black. After cooling, the contents of the tube was dissolved in hot 95% ethanol and allowed to cool. The small quantity of dark orange solid which separated was recrystallized and shown to be A by the identity of its infrared spectrum with that of another sample of A.

(10) Melting points are corrected. Microanalyses were carried out by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and Micro-Tech Laboratories, Skokie, Ill.

(11) M. Dennstedt and J. Zimmerman, *Ber.*, **20**, 1760 (1887).

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 $C_{22}H_2O_2N_2$: 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	253	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

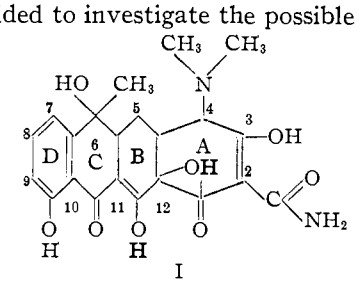
BY EDWARD E. SMISSMAN AND R. BRUCE GABBARD

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.



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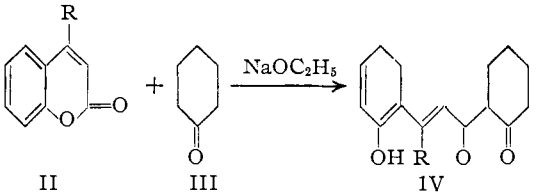

II III IV

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

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