Alicyclic Syntheses. IV. Diels–Alder Additions to 3β,20-Diacetoxypregna-5,16,20-triene[1]

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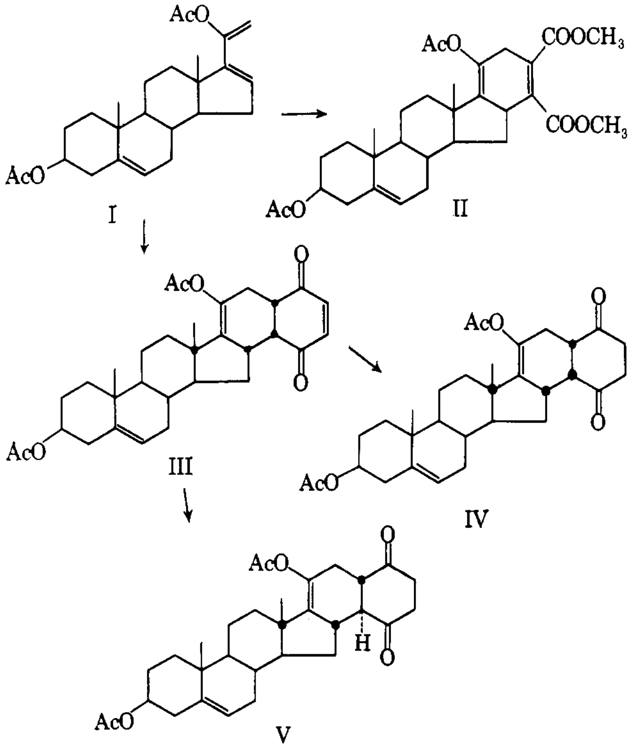
The Diels–Alder reaction of 3β,20-diacetoxypregna-5,16-20-triene (I) with quinone, dimethyl acetylenedicarboxylate, citraconic anhydride, and 5(or 6)-*p*-tolylthiotoluquinone is reported. The adducts with the latter quinone and with quinone itself have been reduced with zinc–acetic acid to yield hexacarbocyclic "extended-steroidal" ring systems. The stereochemical courses of the diene additions and of the reduction process is discussed.

As one phase of our general interest in the synthesis of polycarbocyclic ring systems approaching steroid proportions, we wished to investigate the application of the Diels–Alder reaction to acetoxydienes incorporated in ring systems of already substantial size. Such a system is to be found in 20-acetoxy-16,20-steroid dienes, which are readily obtainable from Δ^{16}-pregnan-20-ones with isopropenyl acetate.[2] While we were interested in the ultimate utility of this reaction scheme for the synthesis of angularly methylated "extended-steroidal" ring systems, the diene addition to the title compound was investigated first with simpler dienophiles.

An earlier patent disclosure indicated that 20-acetoxy-16,20-dienes could add maleic anhydride and *p*-benzoquinone.[3,4] This observation has been confirmed for both additions, and dimethyl acetylenedicarboxylate was found to add to the title compound I as well yielding the pentacarbocyclic adduct II. The addition product[3c] to *p*-benzoquinone is postulated to have the stereochemical configuration shown in III based on the general mode of attack to steroidal centers of unsaturation from the α (β approach hindered by 18 axial angular methyl) side.[5] This will result in a β configuration for the C-16 hydrogen. The *cis* β hydrogens of the newly created ring juncture result from biplanar orientation between the quinone and diene moieties in the transition state resulting in maximum overlap of the π-electron systems.[6] Reduction of adduct III with zinc and acetic acid at room temperature for just a few minutes resulted in the dihydro reduction product IV still represented as having a *cis* E/F ring fusion. When the reduction with zinc was conducted at reflux temperature for 4 hr., a much higher melting (m.p. 305°) isomeric reduction product V was obtained which is considered to possess the *anti–trans* D/E/F ring system. These deductions are based on the investigations of Robins and Walker[7] who ascertained that zinc–acetic acid reductions of dioxoethylenic functions of a few minutes duration and without heat permitted reduction of the ethylenic bond with survival of a *cis* ring juncture, whereas prolonged refluxing resulted in reduction concomitant with isomerization to a *trans* ring fusion. Moreover, while *cis*-α-decalone isomerizes only extremely slowly to *trans*-α-decalone at room temperature,[8] *cis*-1,4-dioxodecalins have been found to be much less stable with respect to their *trans* ring isomers.[9] The difference between isomers IV and V is reflected interestingly enough in their infrared (Nujol mull) spectra in the carbonyl region. While a precise assignment of bands is difficult, the observation was made that *cis* isomer IV has a very strong band at 5.72 (probably due to two acetate carbonyls) and two other strong (but a little weaker than the one at 5.72) bands at 5.81 and 5.90 μ, possibly each due to one of the two ring carbonyls. The *trans* isomer V has an identical band at 5.72 (two acetate carbonyls) and now only *one* other carbonyl (as strong as the 5.72 band) at 5.82 μ, possibly resulting from the two ring carbonyls. The latter coincidence of absorption



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[1] Contribution No. 297 from the Department of Chemistry, Tufts University, Medford 55, Mass.

[2] R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

[3] (a) R. H. Mazur and G. P. Mueller, U. S. Patent 2,753,343; *Chem. Abstr.*, **51**, 2070 (1957). (b) R. H. Mazur, U. S. Patent 2,753,359; *Chem. Abstr.*, **51**, 4436(1957). (c) R. H. Mazur, U. S. Patent 2,812,335; *Chem. Abstr.*, **52**, 6418 (1958).

[4] For a closely related case of Diels–Alder reaction of 20-methyl-16,20-dienes with maleic anhydride, see F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959).

[5] *Cf.* L. F. Fieser, *Experientia*, **6**, 312 (1950).

[6] Rule of maximum accumulation of unsaturation of K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

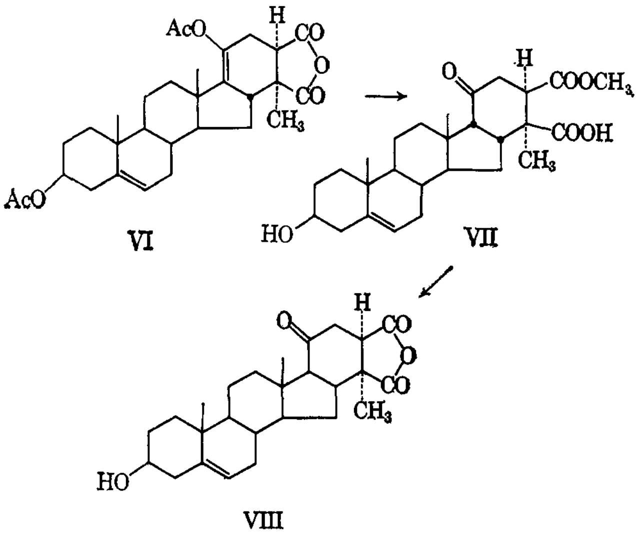
[7] P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954); 177 (1955).

[8] W. Hückel, *Ann.*, **441**, 1 (1925).

[9] R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).

for the ring carbonyls may reflect the circumstance that they are in a comparable environment which a flattened-out all *trans* ring system would afford, while the slightly different positions of absorption for the ring carbonyls in the *cis* isomer might be due to different molecular environment, into which *cis* E/F ring fusion would force them. Molecular models indicate such a difference, and the conclusions drawn above on the stereochemistry of IV and V, based on many previous analogies,[7] find some additional support in this spectral observation.

The ability of the acetoxydiene I to add to methylated dienophiles was investigated next with promising results. When treated with citraconic anhydride in refluxing toluene for 48 hr., an adduct was produced to which we assign the orientation and configuration symbolized in formula VI for reasons presented subsequently. The anhydride VI was hydrolyzed in alkaline methanol to yield what turned out to be a monomethyl ester of the diacid. Although it is not known which way the anhydride was opened, it seems reasonable to indicate attack on the less hindered carbonyl leading to structure VII. A *cis* D/E ring junction is considered more likely to have been produced in the ketonization at C-20, since otherwise there would result two *trans* fused cyclohexane rings on ring D which appear very strained on models. The carbonyl functions on VII are apparently still *cis*, since the compound on being heated is readily changed to a very high-melting (over 300°) anhydride VIII.

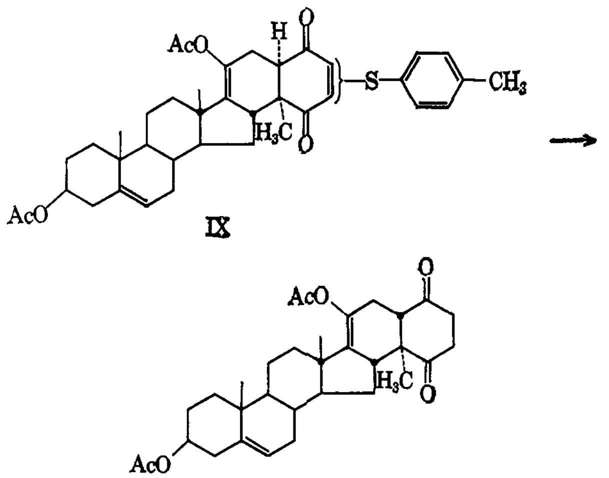


VI

VII

VIII

To append an angularly methylated decalin ring system at position 16,17 on the steroid nucleus the Diels–Alder reaction of the diene I was conducted with 5(or 6)-*p*-tolylthiotoluquinone. The latter dienophile, as well as 5- and 6-methylmercaptotoluquinone, have been shown in allied investigations[10] to yield angularly methylated polycarbocyclic ring systems with dienes when the diene addition is succeeded by zinc–acetic acid reduction; and so, in the present case, an adduct resulted which is portrayed as IX. The orientational course of this Diels–Alder reaction and the *anti–cis* stereochemistry of the D/E/F ring system is discussed subsequently. The infrared spectrum of IX indicated, in addition to the acetate carbonyl absorption at 5.73, a set of carbonyl bands at 5.88, 5.96, and 6.40 μ characteristic of the thio-substituted enedione chromophore in IX.[11] Zinc–acetic acid reduction over an 18-hr. period afforded a reduction product, the hexacarbocyclic dione X (similar infrared carbonyl absorption with that of compound V). The *trans* E/F ring system is assigned on the same basis as that used previously in connection with the E/F configuration of structure V as well as on the experimental evidence available from a parallel investigation of the course of reduction of the butadiene-6-methylmercaptotoluquinone adduct resulting in *trans*-9-methyl-Δ^6-octalin-1,4-dione.[11,12] The prolonged hot acid exposure to X during the conversion of IX to X almost certainly ensures that X possesses the most stable *trans* E/F fusion.



IX

X

Lastly, the orientation of the methyl group in and the stereochemical configuration of the angular methylated adducts VI and IX may be discussed. These assignments follow from (1) *a priori* consideration of the best transition state together with support by analogy to previously established results with similar Diels–Alder reactions, and (2) a departure from the *endo* addition precept of Alder–Stein[6] recognized as operative in those reactions requiring the forcing conditions[13] (higher reaction temperatures and prolonged reaction times), which were necessary to the generation of adducts VI and IX. With respect to this latter point (2), it may be said that *endo* addition has been encountered in Diels–Alder reactions with the more reactive and less encumbered dienophiles such as maleic anhydride[13] and quinone. In the case particularly germane to our discussion of VI and IX, of addition of citraconic anhydride[13c] and 2,6-xyloquinone[13a] to 1-(1-acetoxyvinyl)cyclohexene (both requiring long periods of heating) the products were

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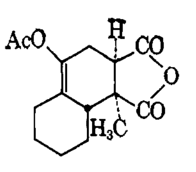
[10] (a) V. Georgian and J. Lepe M., papers I and II of this series, *J. Org. Chem.*, **29**, 1, 40, 45 (1964); (b) V. Georgian and L. L. Skaletzky, paper III of this series, *J. Org. Chem.* **29**, 51 (1964).

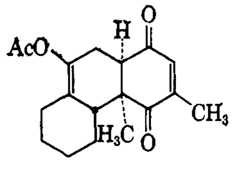
[11] L. L. Skaletzky, Ph.D. dissertation, Northwestern University, 1959. Similar absorption was shown by butadiene adduct of *p*-tolylthiotoluquine.

[12] Paper III of this series, ref. 10b.

[13] (a) M. F. Ansell and G. T. Brooks, *J. Chem. Soc.*, 4518 (1956); (b) J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948); **32**, 1572 (1949); (c) F. Winternitz and C. Balmossiere, *Tetrahedron*, **2**, 100 (1958); (d) I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Dokl. Akad. Nauk SSSR*, **102**, 751 (1955); (e) I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **67**, 77 (1955); *Chem. Abstr.*, **50**, 1713 (1956); (f) I. N. Nazarov, V. F. Kucherov, V. M. Andreyev, and G. M. Segal, *Dokl. Akad. Nauk SSSR*, **104**, 729 (1955); *Chem. Abstr.*, **50**, 11, 304 (1956).



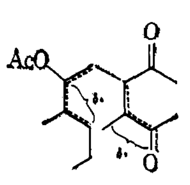
XI



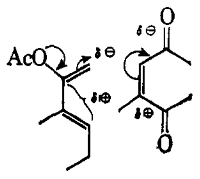
XII

those resulting from *exo* addition and bear the configurations shown in XI and XII, respectively.

Concerning the 1,4 relationship of the angular methyl to the acetoxyl group, point 1, the preceding examples of the synthesis of XI and XII indicate quite clearly the orientational course taken by Diels–Alder reactions of the type leading to VI and IX as well. An understanding of the reason for this directional control may be had in considering a picture for the transition state in these reactions, pictured synoptically as in XIII.[14,15] Association of the addends in this manner will lead to a transition state involving the establishment of the initial bond[15] between the termini of the olefinic systems with electron delocalization at a secondary carbon and a tertiary carbon α to oxygen in the diene and at a tertiary carbon α to carbonyl in the dienophile. Combination of the components alternate to that shown in XIII would lead to higher energy transition states. Similar analysis may be made of the systems leading to the postulation of structures VI and IX. In suggesting acceptance of the validity of these conclusions, we wish to draw attention to the significant fact that the established closely related structures of XI and XII are contrary to those which would have been predicted purely on polar grounds,[16] *e.g.* XIV.



XIII



XIV

Experimental[17]

3β,20-Diacetoxypregna-5,16,20-triene (I).—This substance was prepared essentially according to the published procedure[2] from 16-dehydropregnenolone acetate.

Adduct of I and Maleic Anhydride.—A solution of 4.0 g. of diacetoxypregnatriene I and 1.0 g. of maleic anhydride in 100 ml. of dry benzene was refluxed 4 hr. Some of the benzene was boiled off until crystallization commenced, and after being cooled somewhat, white crystals, 3.4 g., m.p. 245–254°, were filtered and washed with 1:1 benzene–hexane. The product could be recrystallized from chloroform–cyclohexane or from benzene–cyclohexane, m.p. 254–256° (lit.[3a] m.p. 241–243°). Infrared spectra showed in addition to strong acetate carbonyl absorption at 5.73, the characteristic pattern of a five-membered anhydride with carbonyl bands at 5.40 (w), 5.60 μ (s).

Anal. Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 70.06; H, 7.11.

Adduct II of I and Dimethyl Acetylenedicarboxylate.—A solution of 8.0 g. of 3β,20-diacetoxypregna-5,16,20-triene (I) and 3.0 g. of dimethyl acetylenedicarboxylate in 200 ml. of dry benzene was refluxed 8 hr. After the reaction was stripped of volatile matter on a rotary evaporator with steam bath heat, the white crystalline residue was recrystallized from ethyl acetate to yield 6.3 g. of adduct II, m.p. 113–114°. The infrared spectra showed three bands at 5.60, 5.68, and 5.75 and a weak double bond at 6.26 μ.

Anal. Calcd. for $C_{31}H_{40}O_8$: C, 68.87; H, 7.46. Found: C, 68.82; H, 7.22.

Adduct III of I with *p*-Benzoquinone.—A solution of 4.0 g. of 3β,20-diacetoxypregna-5,16,20-triene and 1.0 g. of *p*-benzoquinone in 100 ml. of dry benzene was refluxed 4 hr. The benzene solution was concentrated to the point of incipient crystallization, treated with Norit, and brought to a saturation point with hexane. On being cooled, substance III was produced, 3.6 g., m.p. 227–228°. Recrystallization raised the melting point to 228–229°. Infrared absorption showed ester carbonyls at 5.73 and ketone carbonyl at 5.93, and a double C–OAc stretch band at 8.06–8.16 μ.

Anal. Calcd. for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.82; H, 7.50.

Zinc–Acetic Acid Reduction of III for a Short Period (*cis* Compound IV).—A mixture of 1.0 g. of quinone adduct III in 50 ml. of glacial acetic acid plus 1.0 g. of zinc dust was stirred at room temperature for 15 min. Chloroform (60 ml.) was added; the mixture was filtered and treated with aqueous carbonate solution to neutralize the acetic acid. The chloroform solution was separated, dried (sodium sulfate), and evaporated. The crystalline residue was recrystallized from benzene–hexane or from ethanol to yield IV, m.p. 247–247.6°. Infrared spectra showed no OH bands, and carbonyl absorption at 5.72 (vs), 5.81 (s), 5.90 (s), broad C–OAc stretch band at 8.1–8.2 μ.

Anal. Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 72.90; H, 7.64.

Vigorous Reduction of III with Zinc–Acetic Acid (*trans* Compound V).—A mixture of 0.5 g. of adduct III in 30 ml. of glacial acetic acid and 0.5 g. of zinc dust was refluxed for 4 hr. The hot reaction mixture was diluted with sufficient ethyl acetate to contain the product in solution (*ca.* 100–125 ml.). The filtered solution was evaporated somewhat to the point of crystallization and then allowed to cool. The filtered product V was recrystallized from chloroform–cyclohexane, m.p. 305–307°. Infrared spectra showed no OH bands, carbonyl bands at 5.73 (vs) and 5.82 (vs), C–OAc stretch bands at 8.05 and 8.24 μ.

Anal. Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 73.22; H, 7.77.

Adduct of I with Citraconic Anhydride (Substance VI).—A solution of 4.0 g. of diene I and 1.12 g. of citraconic anhydride[18] in 80 ml. of pure toluene was refluxed for 48 hr. The solvent was removed *in vacuo* and the residue was recrystallized from chloroform and then from ethyl acetate to yield the adduct VI, 2.2 g., m.p. 283–283.4°. Infrared absorption was shown for strong acetate carbonyl at 5.73 and for the characteristic five-membered anhydride pattern at 5.40 (w) and 5.60 μ (s).

Anal. Calcd. for $C_{30}H_{38}O_7$: C, 70.56; H, 7.50. Found: C, 70.26; H, 7.37.

Methanolysis of VI to Half Methyl Ester VII.—A solution of 0.50 g. of citraconic anhydride adduct VI in 50 ml. of dry methanol was treated with two sodium hydroxide pellets and heated at reflux for 45 min. The methanol was stripped *in vacuo* and the solid residue was taken up in a little water and acidified with hydrochloric acid. The precipitated product was filtered and recrystallized from methanol to yield VII. The melting behavior of this substance was erratic as upon gradual heating it

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(14) For additional and more detailed discussion of and references to this subject of Diels–Alder additions between unsymmetrical addends, see ref. 10a.

(15) Recent evidence has accumulated which indicates that, while Diels–Alder reactions may involve transient intermediates in which one bond has been formed [R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); and R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 2198 (1961)], the intermediacy of a triplet biradical has been ruled out [N. J. Turro and G. S. Hammond, *ibid.*, **84**, 2841 (1962)] and is not to be read into formula XIII.

(16) Many previously recorded cases involving unsymmetrical addends conform to this same ostensible anomaly. Accordingly, it has proved fruitful, in accounting for products, to treat such cases, even those wherein polar factors appear to suffice, in terms of the single electron delocalization used in the previous. For an extensive study of Diels–Alder reactions between unsymmetrical addends consult the series of papers by Alder, *et al.*, *Ber.*, **86**, 1372 (1953), also paper I in this series, and references contained therein, (see ref. 10a).

(17) All melting points are uncorrected. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 21 spectrophotometer. Elemental analyses were performed by the microanalytical laboratory of the Smith, Kline and French Laboratories, Inc.

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 140.

tended to go to the anhydride VIII. Gradual heating produced a m.p. 287–290° with a change indicated at *ca.* 235–240°. When placed in a preheated bath at 270°, there was an immediate melting with gas evolution, and when the sample was removed thereafter resolidification took place to a material which then did not melt below 300°. Infrared spectra of VII showed only ketone and acid (ester) carbonyl absorption at 5.75, 5.85, whereas an infrared spectra taken on a crude melt of VII indicated the five-membered anhydride carbonyl pattern with bands at 5.40 (w) and 5.60 μ (s).

Anal. Calcd. for $C_{27}H_{38}O_6 \cdot H_2O$: C, 68.20; H, 8.48. Found: C, 68.16, H, 8.44.

Adduct of I with 5(or 6)-*p*-Tolylthiotoluquinone (Product IX).—A solution of I (4 g.) and 2.5 g. 5(or 6)-*p*-tolylthiotoluquinone in 80 ml. of toluene, containing a pinch of hydroquinone was refluxed 48 hr. The toluene was then removed *in vacuo* and the residue was recrystallized from benzene–hexane to afford 2 g. of pale yellowish white crystals (IX), m.p. 300–302°. The infrared absorption of IX indicated ester carbonyls at 5.70–5.73 and ketone bands at 5.88 and 5.96 μ; in addition a band at 6.40 μ (ms) is characteristic of thio-substituted enedione.[11] Also evident were C–OAc stretching bands at 8.05 and 8.23 μ.

Anal. Calcd. for $C_{39}H_{46}O_6S$: C, 72.87; H, 7.21. Found: C, 72.73; H, 7.03.

Zinc–Acetic Acid Reduction of Compound IX (Product X).—A mixture of 1.0 g. of adduct of the acetoxytriene and 5(or 6)-*p*-tolylthiotoluquinone, 80 ml. of 95% acetic acid, and 6.0 g. of zinc dust was refluxed for 14 hr. The filtered solution together with acetic acid washings was evaporated on the steam bath with a rotary evaporator, and the residue was taken up in chloroform, washed with bicarbonate solution and saturated sodium chloride solution, and dried (sodium sulfate). The dark residue remaining after the chloroform removal was recrystallized from dilute ethanol and once again from ethanol to yield X as white needles, m.p. 241–242°.

Anal. Calcd. for $C_{32}H_{42}O_6$: C, 73.50; H, 8.10. Found: C, 73.64; H, 7.92.

Acknowledgment.—We wish to acknowledge with thanks supplies of steroidal starting material from the Julian Laboratories, Inc., and Smith Kline and French Laboratories.

Acridizinium Derivatives from Hydroquinone Dimethyl Ether

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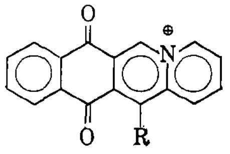
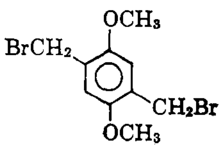
The reaction of an excess of picolinaldoxime with 2,5-bis(bromomethyl)-1,4-dimethoxybenzene affords a salt which can be cyclized (and oxidized) to yield 4a,11a-diazoniapentacene-6,13-quinone dibromide. 2,5-Dimethoxybenzyl bromide, and a quaternary salt prepared therefrom, both undergo bromination in position 6.

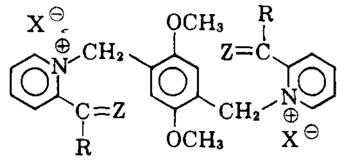
Recently[2] it was shown that 2-bromomethyl-1,4-dimethoxynaphthalene could be converted to quinolizinium derivatives (I), the first examples of quinones in the quinolizinium series. The present communication describes the results of our experiments with bromomethyl derivatives of hydroquinone dimethyl ether.



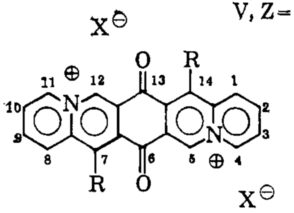
I



II



III, Z = NOH; R = H
IV, Z = O(CH₂)₂O; R = H
V, Z = O; R = C₆H₅



VI, R = H
VII, R = C₆H₅

2,5-Bis(bromomethyl)-1,4-dimethoxybenzene (II), obtained by bromomethylation of the hydroquinone ether, was diquaternized by reaction with picolinaldoxime. The diquaternary salt (III, X = Br) was made to undergo a double cyclization and air oxidation by heating for 24 hr. at 100° in 48% hydrobromic acid. Similar results were obtained when the bisbromomethyl compound (II) was diquaternized with 2-(1,3-dioxolan-2-yl)pyridine[3] and the salt (IV) cyclized.

The yellow 4a,11a-diazoniapentacene-6,13-quinone (VI) dibromide is not only extremely insoluble in common solvents, but like the related 6a-azonianaphthacenequinone salts[2] is attacked by most polar solvents to yield a blue solution. The analytical sample was prepared by crystallization from a trifluoroacetic–acetic acid mixture. No method was found for the purification of the perchlorate or picrate.

In order to obtain further analytical evidence for the existence of the new quinone system, the diphenyl derivative (VII) was prepared. Quaternization of 2,5-bis(bromomethyl)-1,4-dimethoxybenzene (II) with 2-benzoylpyridine occurred in only 18% yield, but the cyclization–oxidation of the salt (V) occurred in greater than 50% yield.

The ultraviolet absorption spectra (Table I) of the new salts in both neutral and acidified solutions in methanol indicate that the attack of the solvent under neutral conditions upon the aromatic system of the quinone (VI and VII) must be more extensive than was observed with 6a-azonianaphthacenequinone salts.[2]

While 2-bromomethyl-1,4-dimethoxybenzene may be isolated from the reaction products obtained in the

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[1] This research was supported by a research grant (NSF-G 19901) of the National Science Foundation. Taken in part from a thesis submitted in partial fulfillment of the requirements for the Ph.D. degree, Duke University.

[2] C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **28**, 1669 (1963).

[3] C. K. Bradsher and J. C. Parham, *ibid.*, **28**, 83 (1963).