The Use of Homolytic, Steric, and Hydrophobic Constants in a Structure–Activity Study of 1,3-Benzodioxole Synergists[1]

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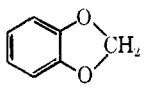
From a study of the structure–activity relationship in a series of 1,3-benzodioxole synergists for the insecticide carbaryl in flies using substituent constants and regression analysis, it is concluded that the synergists may react with an enzyme to produce free radicals which bind tightly to the enzyme inhibiting its detoxifying action on insecticides. Electronic substituent effects parallel those for homolytic arylation. The hydrophobic character of the synergists is quite important and, for maximum activity, log P is about 4. It is also shown that the decrease in activity which occurs when large groups are placed next to the strongly activating nitro group can be quantitatively accounted for by the use of Taft's E_s parameter.

In continuing our study of structure–activity relationships in biochemical systems,[3] this report is concerned with the work of Wilkinson[4] on the synergistic activity of 1,3-benzodioxoles with the insecticide carbaryl (1-naphthyl-*N*-methylcarbamate) in female houseflies. In a recent review Metcalf[5] has assembled evidence which indicates that these synergists operate by inactivating microsomal enzymes which metabolize the insecticides. Insecticides are apparently deactivated by microsomal enzymes in much the same way drugs are deactivated by mammalian microsomes.[6] Our success[7] in correlating McMahon's demethylation studies encouraged us to attempt an analysis of Wilkinson's results. It seems to us that information obtained from a study of these synergists might be useful in designing drug potentiators.

Carbaryl is relatively nontoxic to flies under ordinary conditions;[4] however, it becomes quite toxic when certain methylenedioxy derivatives (I) are added with



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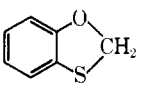

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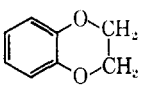

III

it. This effect of methylenedioxy derivatives is not limited to carbaryl but also occurs with other insecticides.[5,8,9] A number of structure–activity studies[5] on various modifications of I have uncovered important molecular requirements for synergist activity. Up to the present, the only functional group approaching methylenedioxy in activity was the sulfur analog II. The ring structure III has very low activity. Replacing the methylenedioxy function with two methoxy groups greatly reduces activity. At least one hydrogen atom on the methylene bridge is necessary for activity. Replacement of both hydrogens by oxygen or methyl groups destroys all activity. Replacement of hydrogen by deuterium reduces activity. This observation, among others, led Hennessy[10] to suggest that loss of one of these hydrogens in the form of a hydride ion yields a biochemically active benzodioxolium ion.

In the stochastic approach to structure–activity problems in biochemical systems, we have found eq 1 to be a useful point of departure.[11] In eq 1, BR represents a standard biological response, π is a hydrophobic bonding constant,[12] and σ is an electronic term. We have found Hammett constants[13] to be most useful in this term. In this report we have applied eq 1 and its simpler as well as more complex forms to the problem of the synergistic activity of the 1,3-benzodioxoles.

$$\log \mathrm{BR} = -k\pi^2 + k'\pi + \rho\sigma + k'' \qquad (1)$$

Method

In the work at hand, BR = SR where SR is the weight/weight synergistic ratio of the LD_{50} of carbaryl in the absence and presence of synergist.[4] That is, SR = [LD_{50} of carbaryl alone]/[LD_{50} of carbaryl + synergist]. Unfortunately, it is not possible to put the data on a molar basis. For most of the synergists this is not a serious consideration since variation in ratios due to variations in weight/weight rather than mole/mole will probably be less than the variations in the biological testing. However, a few of the molecules with high molecular weight will appear to be less active on a weight basis than on a molar basis. Table I contains data on 16 molecules for which substituent constants are available. For our first exploratory work, molecules 12, 13, and 14 were not included since it was felt that steric hindrance of large groups next to the nitro group would hinder its electronic interaction with the ring electrons.

The results obtained using σ, σ^+, and σ_1 in eq 1 (eq 8–10) were not as good as one might expect. From previous work[6,7] it occurred to us that the inhibitors might operate through a radical mechanism. In particular, we were struck by the observation of Wilkinson[4] that the introduction of almost any substituent on the

(1) This work was supported by Research Grant GM-07492 from the National Institutes of Health.

(2) John Simon Guggenheim Fellow 1966–1967.

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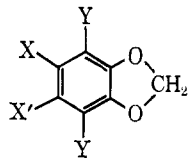
(12) (a) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

(13) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE I
OBSERVED AND CALCULATED SYNERGISTIC ACTIVITY OF 1,3-BENZODIOXOLES WITH CARBARYL IN FLIES

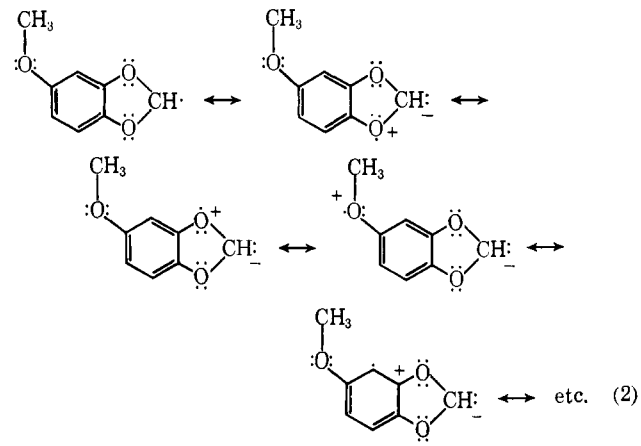


No.	X	X′	Y	$\Sigma\pi$ [a]	$\Sigma\sigma'$ [b]	$\Sigma\sigma_p$ [c]	$\Sigma\sigma_1$ [d]	$\Sigma\sigma^-$ [d]	E_s [e]	Obsd[f] log SR5	Calcd[g] log SR5
1	H	H	H	00	00	00	00	00	00	1.49	1.586
2	H	CH_3	H	0.52	0.09	−0.17	−0.03	−0.31	00	1.93	2.029
3	H	Cl	H	0.70	0.03	0.23	0.42	0.11	00	1.88	2.023
4	H	Br	H	1.02	0.11	0.23	0.45	0.15	00	2.19	2.252
5	H	NO_2	H	0.24	0.47	0.78	0.68	0.79	00	2.48	2.430
6	H	OCH_3	H	−0.04	0.40	−0.27	0.28	−0.78	00	2.44	2.141
7	Cl	Cl	H	1.40	0.06	0.46	0.84	0.22	00	2.28	2.258
8	Br	Br	H	2.04	0.22	0.46	0.90	0.30	00	2.44	2.489
9	Cl	OCH_3	H	0.66	0.43	−0.04	0.70	−0.67	00	2.62	2.590
10	Br	OCH_3	H	0.98	0.51	−0.04	0.73	−0.63	00	2.66	2.824
11	NO_2	OCH_3	H	0.20	0.87	0.51	0.96	0.01	−0.25	2.73	2.770
12	NO_2	Cl	H	0.94	0.50	1.01	1.10	0.90	−1.06	2.11	1.870
13	NO_2	Br	H	1.26	0.58	1.01	1.13	0.94	−1.24	1.92	1.910
14	NO_2	NO_2	H	0.48	0.94	1.56	1.36	1.58	−1.99	1.38	1.509
15	Cl	Cl	Cl	2.80	0.12	0.92	1.68	0.44	00	2.34	2.121
16	Br	Br	Br	4.08	0.44	0.92	1.80	0.60	00	1.59	1.677

[a] π values are from the phenoxyacetic acid system.[12a] [b] See text for definition of σ'. [c] From ref 13. [d] From C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 334 (1964). [e] For only compounds **11**–**14** did it seem appropriate to use this constant. See discussion under method. [f] From ref 4. SR5 represents data from experiments where the ratio of synergist to insecticide was 5:1. [g] Calculated using eq 7.

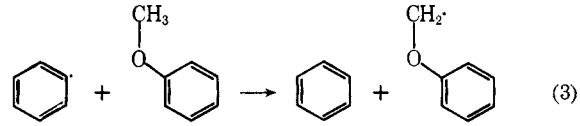
benzene ring gave derivatives of increased activity. This is a well-known characteristic of substituent effects on homolytic reactions with aromatic compounds.[14]

The two most activating substituents in Table I are the nitro and methoxy functions. It is well known that in nucleophilic or electrophilic substitutions these functions have *opposite* effects. However, in certain homolytic substitutions, nitro and methoxy are among the strongest promoters of reaction.[15] Relatively little work has been done using the Hammett equation for homolytic reaction. Leffler and Grunwald[16] point out that sometimes radical reactions can be correlated using σ. Pryor[17] has pointed out that in a number of instances substituent effects for electrophilic radicals are correlated by σ^+. The fact that we did not obtain a very high correlation using σ^+ appeared to indicate that an electrophilic-type radical might not be involved in our system and that it might be profitable to formulate a Hammett-like constant from the relative rates of phenylation obtained by Hey and Williams[15,18] for compounds of the type C_6H_5X. For the substituent X, σ' is defined as $\log {}^{PhX}_{PhH}K$ where K is the relative phenylation rate[14] for all positions on PhX. Since in our example of the 1,3-benzodioxoles each substituent is situated *para* to one and *meta* to the other methylenedioxy function, it seems more appropriate to use the total rate constant K rather than a partial rate constant for a *meta* or *para* position. Equation 2 illustrates how the methylenedioxy function is admirably constructed to delocalize an odd electron resulting from the homolytic removal of a methylene hydrogen and how a methoxy group could participate in this process. The value[15] of σ' for OCH_3 represents an



(2)

uncorrected value in which some attack of the type depicted in eq 3 would make ${}^{PhOCH_3}_{PhH}K$ a little higher than that corrected for attack on the ring only. For our purposes this is very likely an advantage since the methoxyl group on the benzodioxole ring could react in a parallel manner in the biochemical system.



(3)

A rather successful approach for correlating substituent effects in radical reactions has been recently developed by Yamamoto and Otsu.[19] These workers have shown that the relationship, $\log (k/k_0) = \rho\sigma + \gamma E_R$ can be used to correlate a variety of radical

(14) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960.
(15) Reference 14, p 57.
(16) J. E. Leffler and R. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 171.
(17) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, Chapter 12.
(18) G. H. Williams, *Chem. Ind.* (London), 1286 (1961).
(19) T. Yamamoto and T. Otsu, *ibid.*, 787 (1967).

reactions. In this relationship σ is the usual Hammett constant and E_R values were obtained from the hydrogen abstraction reaction of nuclear-substituted cumenes. The following E_R values have been employed by us in deriving eq 17 and 18: H, 0.00; CH_3, 0.03; Cl, 0.10; Br, 0.12; NO_2, 0.41; OCH_3, 0.11.

After obtaining a good correlation omitting **12–14** in Table I (see eq 7), it seemed of interest to see if these molecules could be included by taking into account the decoupling of resonance of the nitro group and the ring by large *ortho* substituents. For this purpose we have employed Taft's E_s constants obtained from the hydrolysis of *o*-benzoates.[16] Unfortunately, Taft has not reported a value for H. We have elected to place E_s on a basis relative to H by subtracting the constant 1.24 for aliphatic H from E_s as determined in *o*-benzoates.[20] We assume this defines E_s for H in our system as 0. We also assume there are no other significant steric inhibitions of resonance. While the value of 1.24 for H is only a rough approximation, this is fortunately not serious since the results with eq 14 are not very sensitive to changes in the figure of 1.24. If we use a value of 1.00 instead, the coefficient with E_s in the resulting equation is 0.969 and r is 0.943. If we use the value of 1.48, the coefficient for E_s is 0.778 and r is 0.933. Neither of these coefficients is far from the value of 0.851 of eq 14.

Results and Discussion

From the data in Table I we have derived eq 4–7 by the method of least squares. In these equations SR5 refers to the data in which the ratio of synergist to insecticide was 5:1, n stands for the number of data points used in the regression, and s represents the standard deviation from regression. Compounds **12–14** were not included for reasons discussed under the Method Section. σ^+ is a radical constant defined in the section on method. Equations 4–6 give poor correlations. Adding an electronic term to eq 6 yields eq 7 which gives a very good correlation, accounting for 86% of the variance in the data. Taking the partial derivative, $\partial \log SR5/\partial\pi$, and setting this equal to zero, gives a value of 1.72 (1.41–1.96) for π_0. This represents the ideal lipophilic character for the sum of the substituents.[3] The figures in parentheses define the 95% confidence interval on this constant. The positive coefficient with σ^+ indicates that the electronic aspect of the substituent effect parallels that of the homolytic phenylation of simple benzene derivatives.

	n	r	s	
$\log SR5 = 0.940\sigma^+ + 1.963$	13	0.603	0.334	(4)
$\log SR5 = 0.070\pi + 0.917\sigma^+ + 2.050$	13	0.638	0.338	(5)
$\log SR5 = -0.115\pi^2 + 0.348\pi + 2.146$	13	0.500	0.380	(6)
$\log SR5 = -0.195\pi^2 + 0.670\pi + 1.316\sigma^+ + 1.612$	13	0.929	0.171	(7)

Equations 8–10 are comparable to eq 7 except in these we have examined the possibility that the electronic effects might be better described by σ_μ, σ_I, or σ^-. Much poorer correlations result using these parameters.

	n	r	s	
$\log SR5 = -0.119\pi^2 + 0.296\pi + 0.289\sigma_\mu + 2.126$	13	0.544	0.388	(8)
$\log SR5 = -0.128\pi^2 + 0.032\pi + 0.945\sigma_I + 1.851$	13	0.852	0.242	(9)
$\log SR5 = -0.113\pi^2 + 0.374\pi - 0.166\sigma^- + 2.184$	13	0.532	0.392	(10)

The best of these three equations (9) accounts for only 73% of the variance in log SR5.

It occurred to us that using an additional term in eq 7 to account for the perturbation of the nitro group by the *ortho* substituents would allow us to include molecules **12–14** in our analysis. Accordingly, we have derived eq 11 and 12. Including the three data points in an equation of the form of 7 yields eq 11 which gives a very poor correlation. Equation 12 in which correction is made for steric interaction between the nitro group and functions *ortho* to it by E_s yields as good a correlation as eq 7. It is assumed in eq 12 that steric interactions between *ortho* substituents can be ignored in all of the examples except molecules **11–14**. In all, the E_s value for methoxy is quite small and could be neglected since this compound was included in the formulation of eq 7 and was found to be moderately well fit. The coefficients associated with σ^+ in eq 7 and 12 are quite close as are π_0 values (1.71 for eq 12). This would indicate that the sole effect of the E_s term is to correct for the interaction between the nitro group and the large group *ortho* to it.

	n	r	s	
$\log SR5 = -0.098\pi^2 + 0.318\pi + 0.185\sigma^+ + 1.970$	16	0.359	0.440	(11)
$\log SR5 = -0.206\pi^2 + 0.706\pi + 1.460\sigma^+ + 0.875E_s + 1.586$	16	0.943	0.164	(12)

Equations 13 and 14, comparable to 12, are for experiments done[4] with 1:1 and 10:1 ratios of synergist and insecticide. To conserve space, the experimental data are not included in Table I.

	n	r	s	
$\log SR1 = -0.192\pi^2 + 0.689\pi + 1.671\sigma^+ + 0.909E_s + 1.191$	16	0.941	0.170	(13)
$\log SR10 = -0.201\pi^2 + 0.704\pi + 1.414\sigma^+ + 0.851E_s + 1.709$	16	0.940	0.163	(14)

(20) Reference 16, p 228.

To explore the possibility that higher order equations might give better correlations, we added a term in $\pi\sigma$ to eq 12. A significant reduction in variance was not obtained. The same is true for the addition of a term in σ^2. However, adding two terms does result in a quite significant reduction in variance (eq 15). How much validity can be attached to eq 15 remains to be seen. One would certainly like a good many more data points before making any strong statements about the meaning of the additional terms, especially in view of the fact that neither term alone caused a significant improvement.

$$\log \text{SR5} = -0.123\pi^2 + 0.633\pi - 1.823\sigma'^2 + 3.162\sigma' - 0.796(\pi\sigma') + 0.639E_s + 1.450 \quad n = 16,\ r = 0.991,\ s = 0.074 \quad (15)$$

From a smaller group of compounds (Table II) for which the synergistic ratio was defined in a slightly different fashion, we obtain eq 16. From eq 16 we find $\pi_0 = 1.66$, in good agreement with the other work. However, the confidence interval on this figure cannot be defined.[21] While the coefficient with σ' is much higher for this different type of fly, we cannot say that the difference in σ' is due to the different fly because of the uncertainty in the value of the coefficient with σ'. The 95% confidence interval is wide (± 4.29). This is partly because of the few points and partly because of more scatter in the data.

$$\log \text{SR5} = -0.576\pi^2 + 1.908\pi + 3.501\sigma' + 0.233 \quad n = 6,\ r = 0.934,\ s = 0.404 \quad (16)$$

TABLE II
OBSERVED AND CALCULATED SYNERGISTIC ACTIVITY FOR MONOSUBSTITUTED 1,3-BENZODIOXOLES WITH CARBARYL IN FLIES

Substituent	π	σ'	Obsd[a] log SR5	Calcd[b] log SR5
CH_3O	−0.04	0.40	1.91	1.546
NO_2	0.24	0.47	1.95	2.293
t-Butyl	1.68	−0.06	1.57	1.592
CH_3	0.52	0.09	1.50	1.374
Cl	0.70	0.03	1.48	1.381
H	0	0	0	−0.223

[a] From ref 8. [b] Calculated using eq 17.

It is of interest to compare the results obtained with the single constants σ_p, σ^+, and σ' with the more complex constants ($\sigma + E_R$) of Yamamoto and Otsu (see the Method section). Equations 17 and 18 can be compared with eq 7. In eq 17 we have simply added the resonance interaction term (E_R) to eq 6. While eq 17 does result in considerable reduction in variance, when compared to eq 6 it is not nearly as good as eq 7. Equation 18, containing an additional variable and an additional disposable constant, gives a very slight but not significant improvement over eq 7. While the $\sigma + E_R$ constants have been shown to correlate a variety of radical reactions, we feel that at least in the present instance the greater simplicity of σ' is a distinct advantage. Log P_0 for eq 18 is 1.57 (1.10–1.91), in good agreement with the value obtained from eq 7. The fact that two different sets of radical constants give comparable results for the benzodioxole synergists strongly supports the idea that these molecules are involved in radical reactions.

$$\log \text{SR5} = -0.160\pi^2 + 0.386\pi + 1.883E_R + 1.777 \quad n = 13,\ r = 0.843,\ s = 0.249 \quad (17)$$

$$\log \text{SR5} = -0.180\pi^2 + 0.566\pi + 3.176E_R - 0.847\sigma_p + 1.585 \quad n = 13,\ r = 0.944,\ s = 0.162 \quad (18)$$

In the study by Wilkinson, Metcalf, and Fukuto from which the data in Table II are taken, activities for a large number of derivatives were reported. Unfortunately, substituent constants are not available to analyze their relative activities. From an inspection of these data one is inclined to suspect that flatness of the synergist may be important for maximum activity.

The question arises, what does the fact that electronic effects of substituents in the synergists parallel those in homolytic phenylation mean? As mentioned in the introduction, the hydrogens on the CH_2 group of the methylenedioxy group are strongly implicated in the synergistic action and synergists seem to operate by inhibiting microsomal attack on the insecticides. Thus, it seems that abstraction of a hydrogen by a microsomal enzyme from the synergist according to eq 2 could generate a relatively stable free radical which could act as an inhibitor of a free-radical generating enzyme responsible for oxidation of C–H bonds in lipophilic drugs. A relatively stable radical, if sufficiently lipophilic, could remain bound to an enzyme, thus inhibiting its further action. In the typical enzymatic reaction sequence shown in eq 19 we have found[22] that k_3 can be

$$\text{E} + \text{S} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \text{ES} \xrightarrow{k_3} \text{E} + \text{product} \quad (19)$$

greatly reduced by lipophilic binding between product and E. The great dependence of activity of the synergists on σ' and the rather poor correlations obtained using σ^+ and σ_I would indicate that H removal by homolytic cleavage is a better postulate on which to base discussion than hydride removal suggested by Hennessy.[10]

Turning to eq 12–14, we find π_0 to be 1.71, 1.79, and 1.75, respectively. Taking advantage of the additive character of π and log P we can calculate log P_0, the ideal partition coefficient for a synergist. Log P for 3,4-methylenedioxybenzyl alcohol is 1.05; subtracting log P for benzyl alcohol (1.10) from this yields π (−0.05) for the $-OCH_2O-$ moiety. Addition of this to the log P of benzene (2.13) gives 2.08 for 1 in Table I. Taking π_0 to be 1.75, we find log P_0 of 3.8 for the ideal lipophilic character of a synergist for carbaryl in flies. Keeping in mind that the molecules of highest molecular weight should be rated more active on a molar basis (see the Method section), we would expect log P_0 for the set to be close to 4. It is of interest to note that this is

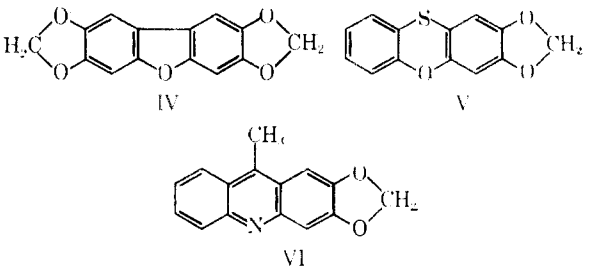
(21) C. Hansch, A. R. Steward, S. M. Anderson, and D. L. Bentley, *J. Med. Chem.*, **11**, 1 (1968).

(22) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Am. Chem. Soc.*, **87**, 2738 (1965).

about the same value we found for log P_0 for a variety of bactericides acting on gram-negative bacteria.[3d] This may not be a particularly useful observation; on the other hand, it could be that in both instances drugs are acting on the same type of cellular organelles and about the same lipophilic character is ideal for penetration in each case.

The big improvement in correlation of eq 12 over eq 11 constitutes another illustration of the use of the steric parameter E_s in a nonhomogeneous biochemical reaction. Our own previous work[3e,21,23] indicates that E_s may be a very important parameter for use in nonhomogeneous systems.

The results contained in the above equations do offer useful information for the synthesis of more potent synergists for insecticides. In the first place, one should design quite lipophilic molecules having log P values near 4. Taking advantage of the additive character[12] of π and log P, such molecules can be designed without the effort of first making them and then measuring log P. A hydrogen atom should be built into such compounds and be so situated that the odd electron generated by its homolytic removal can be stabilized by an extensive π-electron system. Keeping in mind that the $-OCH_2O-$ function has a π value of almost zero, and that log P for dibenzofuran is 4.12, 4.05 for phenothiazine, and 3.9 for methylacridine, IV–VI



IV V

VI

and their isomers would be interesting examples. Many other possibilities come readily to mind.

While the homolytic arylation studies reviewed by Williams and the radical work of Yamamoto and Otsu[19] provide excellent sources for leads in such work, this would appear to be an ideal situation to which molecular orbital theory[24] could be applied in the design of π-electron systems best suited to delocalize an odd electron.

The above work is of course most pertinent to the mechanism of action and design of synergists for insecticides. It would also seem to be of use in our general understanding of the metabolism of drugs since there is considerable evidence that the microsomal action of insects is quite similar to that of mammals. It seems likely that the homolytic constants we have formulated from the work of Hey and Williams should be of use in correlating homolytic reactions in biochemical systems.

(23) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).

(24) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963.

Estra-1,3,5(10),15-tetraenes. I. Birch Reduction

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The addition of organolithium reagents to 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**3**) yielded a series of 17-substituted Δ^{15} derivatives (**6**). Birch reduction of **6a** and **6b** at −78° led to reduction of ring A without reduction of the Δ^{15} double bond. Oppenauer oxidation at room temperature of the intermediate 3-methoxyestra-2,5(10),15-trien-17β-ol (**10**) afforded the ketone **11** which was converted to a series of active progestins. The hypocholesteremic and estrogenic activities of the intermediate aromatic steroids are reported. A simple procedure for ethynylation of base-sensitive ketones is described.

As part of a synthetic program leading to modified steroidal estrogens and their derivatives, some reactions of estra-1,3,5(10),15-tetraenes, in particular 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**3**), were examined.[1] The Δ^{15}-17-one **3** had previously been prepared in five steps from estrone methyl ether (1) by Johnson and Johns.[2] We used essentially the same procedure, but reduced the number of steps to four by direct bromination of estrone methyl ether with $CuBr_2$[3] (Scheme I).

In an effort to reduce the number of steps even further, the direct dehydrobromination of bromo ketone **2** was reexamined. In a related series, Pappo, *et al.*,[4] treated 16-bromo-3β-hydroxyandrostan-17-one acetate with γ-collidine and obtained the Δ^{14}-17-one in 5% yield as the only isolable product. In the present work the use of LiBr and Li_2CO_3 in DMF on **2** at 100°[5] gave little reaction after 21 hr. At 130° a mixture of the Δ^{14}-17-one **4** and the 14β-Δ^{15}-17-one **5** was formed with no significant amount of the less stable unsaturated ketone **3** present.[6] On a preparative scale, 39% of **4** and 38% of **5** were obtained. Use of $CaCO_3$ in dimethylacetamide[7] led to similar results; so, no further shortening of our reaction sequence was accomplished.

(1) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964), have used **3** to prepare a series of 15-substituted derivatives.

(2) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(3) E. R. Glazier, *J. Org. Chem.*, **27**, 4397 (1962).

(4) R. Pappo, B. M. Bloom and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 6347 (1956).

(5) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. France*, 366 (1958).

(6) The instability of 14α-Δ^{15}-17-ones to heat [K. Tsuda, N. Ikekawa, Y. Sato, S. Tanaka, and H. Hasegawa, *Chem. Pharm. Bull* (Tokyo), **10**, 332 (1962)] and to acid [ref 2 and E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 2114 (1964)] has been noted.

(7) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).