[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Alkylation of Cresol Salts. Use of Azo Coupling to Establish Orientation[1-3]

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The sodium salt of *o*-cresol suspended in benzene has been found to react with benzyl bromide to give not only benzyl *o*-cresyl ether (III) and 6-benzyl-2-methylphenol (II) (the product of carbon-alkylation at the unsubstituted *o*-position of the benzene ring) but also 6-benzyl-6-methylcyclohexa-2,4-dienone (I). The sodium salt of *p*-cresol, on the other hand, gives *ortho*- and oxygen-substitution but no 4-benzyl-4-methylcyclohexa-2,5-dienone (V), the product of *para*-substitution, could be detected with ultraviolet or infrared spectroscopy.

In the course of the structure determination of two of the alkylation products they have been coupled with phenyldiazonium acetate and infrared and ultraviolet spectral differences between *o*- and *p*-hydroxyazobenzenes are reported. The ultraviolet spectra indicate further that there is an appreciable difference between *o*- and *p*-hydroxyazobenzenes, the *p*-isomers being stronger acids.

In the course of a study[2,3] of factors which control the position of alkylation of salts of phenols the alkylations of suspensions of the sodium salts of *o*- and *p*-cresol in benzene with benzyl bromide were carried out. The sodium salt of *o*-cresol suspended in refluxing benzene[4] gave 6-benzyl-6-methylcyclohexadienone (I) (11% of theoretical), 2-benzyl-6-methylphenol (II) (28% of theoretical) and *o*-cresyl benzyl ether (III) (28% of theoretical) together with 40% of recovered *o*-cresol. (The yields given here are calculated on the basis of the unrecovered starting material.) The structure of the dienone (I) was confirmed by the ultraviolet and infrared spectra. That the benzylmethylphenol (II) was substituted by the benzyl group in a position *ortho*- to the hydroxyl group was demonstrated by the examination of the ultraviolet and infrared spectra of the derived benzene azo compound (IV). The spectral correlations employed will be discussed later in this paper.

It will be noted that attack of the benzyl bromide appears to be somewhat (a factor of 2–3) slower at an *ortho*-position containing a methyl group than at an *ortho*-position occupied only by a hydrogen atom as might, perhaps, be anticipated on the basis of steric considerations.

The benzylation at 110° with benzyl chloride of *p*-cresol sodium salt suspended in toluene was carried out by Claisen, Kremers, Roth, and Tietze.[4] It was desirable to carry out the reaction under conditions (benzyl bromide, benzene solvent) employed generally in our work, however, and, in particular, modern spectral methods, unavailable to Claisen, provide a sensitive method of detecting even small amounts of the product of *para*-alkylation, 4-benzyl-4-methylcyclohexa-2,5-dienone (V) should it be present. This reaction was therefore carried out under the same conditions which were used for *o*-cresol, above. The principal product was 2-benzyl-4-methylphenol (VI) (62%) as had been found by Claisen. There were, in addition, small amounts of secondary products probably formed by a second benzylation of the product VI. Benzyl 2-benzyl-4-methylphenyl ether (VII) (3%) had not been found by Claisen but 2,6-dibenzyl-4-methylphenol (VIII) (9%) had also been earlier reported.[4] There was also an appreciable amount (17%) of benzyl *p*-cresyl ether (IX). Neither the infrared nor the ultraviolet spectrum of the product showed any evidence of the presence of the dienone (V). The over-all ratio of carbon to oxygen attack is therefore 4.3 or the ratio of substitution at just one of the two *ortho*-positions to substitution on oxygen is 2. It will be noted that the comparable ratio of attack at the free *ortho*-position to attack at oxygen is 1 in the reaction of *o*-cresol discussed above.

Results of these alkylation experiments are summarized in the chart below. Claisen's yields[4] are given in parentheses below the *p*-cresol reaction. It will be noted that, in general, there is very good agreement—an indication that the change from benzyl chloride to benzyl bromide has little effect on the relative amounts of carbon- and oxygen-alkylation.

In establishing the structure of the 2-benzyl-6-methylphenol (II) obtained in the alkylation of *o*-cresol above it was of importance to rule out the possibility that the benzyl group might have entered at the 4-position. A particularly attractive method would take advantage of characteristic differences present in the ultraviolet and infrared spectra of *ortho*- and *para*-hydroxyazobenzenes.

Ultraviolet and visible spectra of certain tolueneazocresols were reported as early as 1927 and differences between the *ortho*- and *para*-isomers were noted.[5] The spectra of 2- and 4-hydroxyazobenzene have been reported.[6,7] More recently the positions

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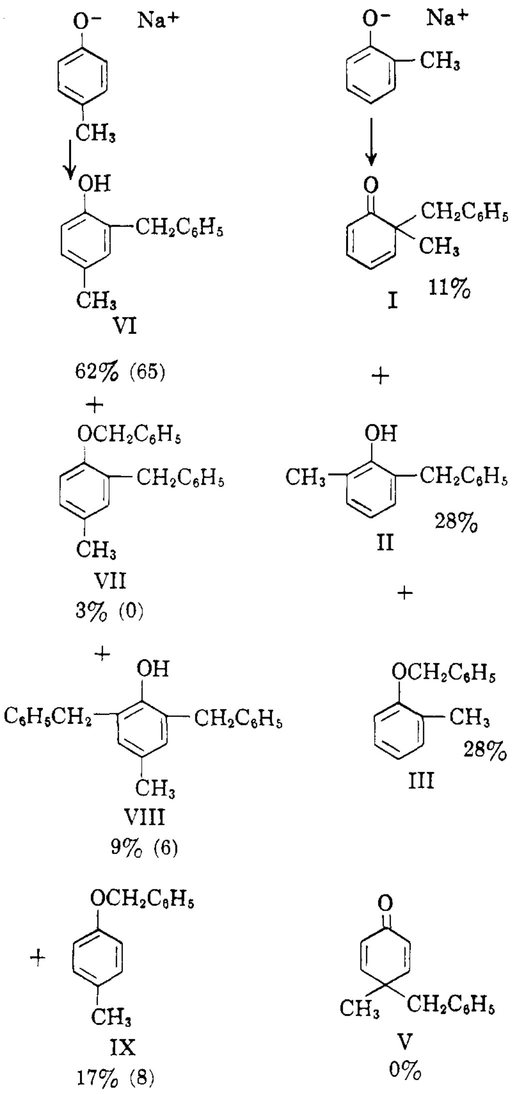
(2) Presented in part at the Fifteenth National Organic Chemistry Symposium of the AMERICAN CHEMICAL SOCIETY, Rochester, N. Y., June, 1957.

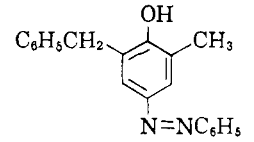
(3) See D. Y. Curtin and Robert J. Crawford, *Chemistry & Industry*, 313 (1956).

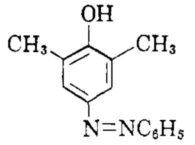
(4) Conditions similar to those employed by L. Claisen, F. Kremers, F. Roth, and E. Tietze, *Ann.*, **442**, 210 (1925) in their studies of the carbon-alkylation of certain phenols.

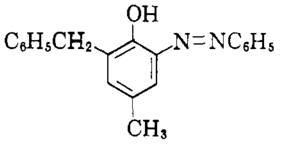


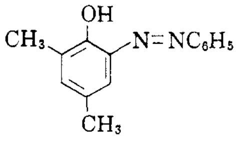
of the visible light absorption maxima of 2-hydroxy-3,5-dimethylazobenzene and 4-hydroxy-3,5-dimethylazobenzene and complete ultraviolet-visible spectra of 4-hydroxyazobenzene and 2-hydroxy-4-methylazobenzene have been published.[8]

2-Benzyl-6-methylphenol (II) and also 2-benzyl-4-methylphenol (VI) obtained in the alkylation reactions above were best converted to the benzeneazo compounds (IV) and (X) by treatment with *N*-nitrosoacetanilide in methanol containing piperidine.[9] As reference compounds, 3,5-dimethyl-2-hydroxyazobenzene (XI) and 4-hydroxy-3,5-dimethylazobenzene (XII) were prepared. The spectra of IV and X are presented in Figs. 1 and 2.


IV


XII


X


XI

The positions and intensities of the principal maxima in those spectra obtained with ethanol solutions are in reasonably good agreement with those reported[8] for 4-hydroxyazobenzene and 4-methyl-2-hydroxyazobenzene in the same solvent. One difference, however, is that the 4-hydroxyazobenzenes (IV and XII) show no maximum in the region around 400 mμ where 4-hydroxyazobenzene showed a shoulder.[8]

The spectra in acetic acid and 0.1*N* sodium hydroxide solution of IV and X are also recorded in Figs. 1 and 2. It is of interest that in 0.1*N* sodium hydroxide the 4-hydroxy compounds (IV and XII) appear to have been converted essentially completely to their anion forms as shown by the complete disappearance of the band at 352 mμ whereas the corresponding band in the spectra of the 2-

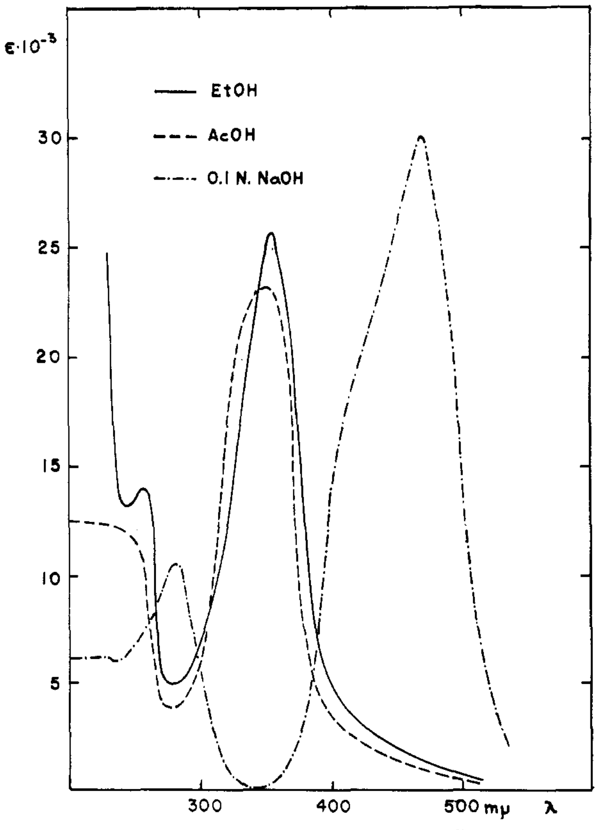


FIG. 1. ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA OF 3-BENZYL-4-HYDROXY-5-METHYLAZOBENZENE (IV).

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(5) T. Uemura and S. Tabei, *Bull. Chem. Soc. Japan*, **2**, 229 (1927).

(6) R. Kuhn and F. Bar, *Ann.*, **516**, 143 (1935).

(7) E. Marder and I. W. Ruderman, *J. Am. Chem. Soc.*, **73**, 5475 (1951).

(8) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 3734 (1952).

(9) R. Huisgen and G. Horeld, *Ann.*, **562**, 137 (1949).

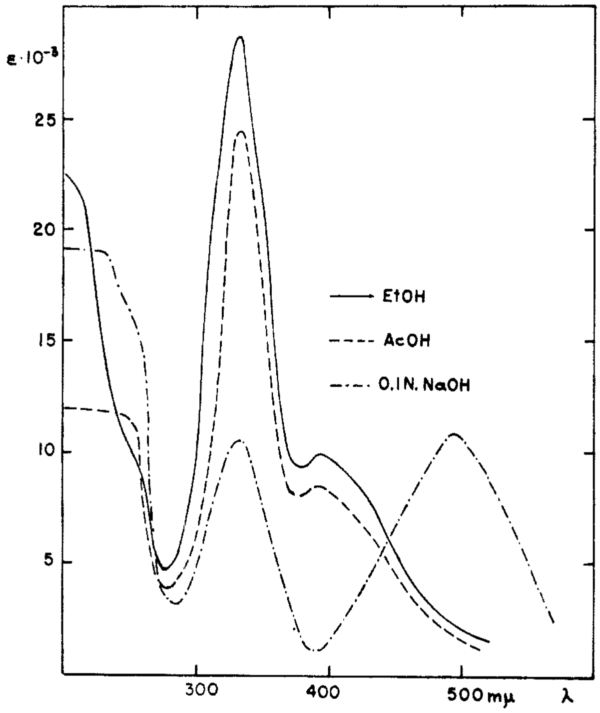

FIG. 2. ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA OF 3-BENZYL-2-HYDROXY-5-METHYLAZOBENZENE (X).

hydroxyazobenzenes (X) and (XI) still has about one third of its original intensity in each case. The conclusion that the *p*-hydroxyazobenzenes are appreciably stronger acids than the *o*-isomers is not unexpected since hydrogen bonding here selectively stabilizes the phenol but not the anion.[10]

It has been pointed out[11] that in the near-infrared (6200–7500 cm.$^{-1}$) *o*-hydroxyazobenzenes (in contrast to the *p*-isomers) because of internal hydrogen-bonding show little or no absorption characteristic of the hydrogen-oxygen stretching frequency (overtone). The infrared spectra (10% chloroform solutions) of the four hydroxyazobenzenes prepared in the present work verify this observation. The two *p*-hydroxyazobenzenes (XII and IV) show strong hydroxyl absorption at 3600 cm.$^{-1}$ whereas the *o*-hydroxy compounds (X and XI) have no absorption at 3600 cm.$^{-1}$ but, instead, have diffuse hydroxyl absorption spread over the region from 3100 to 2200 cm.$^{-1}$ A second point of interest is that the two *p*-hydroxy compounds have a single strong absorption at 1600 cm.$^{-1}$ (comparable in intensity to the 690-cm.$^{-1}$ monosubstituted phenyl band) whereas in the *o*-hydroxy compounds this absorption occurs as a doublet (1587, 1608 cm.$^{-1}$). It seems likely that this is the nitrogen-nitrogen double bond[12] stretching frequency which occurs at somewhat variable position in the *o*-hydroxyazobenzenes because they exist as mixtures of isomers with variable degrees of hydrogen bonding.

EXPERIMENTAL[13]

Alkylation of o-cresol. A suspension of the sodium salt of *o*-cresol was prepared by the reaction of 4.6 g. (0.2 mole) of sodium with 21.6 g. (0.2 mole) of *o*-cresol in 350 ml. of boiling benzene. After formation of the sodium salt was completed, 72 ml. (0.6 mole) of benzyl bromide was added and the mixture was heated under reflux for 6 hr.

The reaction mixture after dilution with 200 ml. of petroleum ether (b.p. 30–60°) was separated into a phenolic and a neutral fraction by extraction with Claisen's alkali (potassium hydroxide, 350 g./l. of solution; water, 250 ml./l. of solution; in methanol). Distillation of the neutral fraction separated 43.7 g. of unreacted benzyl bromide (b.p. 82–85°/15 mm.) and 11.5 g. of residue. The residue was shown by a comparison of the ultraviolet and infrared spectra with those of the components separated as described below to contain (6.5 g.) 57% of benzyl *o*-cresyl ether (III) (absorption in cyclohexane at 1199 cm.$^{-1}$) and 2.5 g. (22%) of 6-benzyl-6-methyl-2,4-cyclohexadienone (I). A portion (5 g.) of the neutral fraction in 50 ml. of hexane was chromatographed on 150 g. of Merck aluminum oxide. Elution with 700 ml. of hexane yielded 2.9 g. (17% of the theoretical yield of 28% based on unrecovered phenol) of benzyl *o*-cresyl ether (III), which on distillation had b.p. 110°/0.01 mm. The ultraviolet spectrum (in cyclohexane) showed maxima at 272 mμ (ϵ 1.95 × 10^3) and at 278 mμ (ϵ 1.83 × 10^3).

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.82; H, 7.18.

6-Benzyl-6-methyl-2,4-cyclohexadienone (I) (1.1 g., 6% or 11% based on unrecovered phenol) of yellow oil, b.p. 104–105°/0.05 mm. was eluted from the column with 500 ml. of hexane-ether (9–1). The ultraviolet spectrum (in cyclohexane solution) had a maximum at 298 mμ (ϵ 4.17 × 10^3). The infrared spectrum (10% benzene solution) shows a strong carbonyl absorption at 1672 cm.$^{-1}$ together with a weaker band at 1639 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.61; H, 7.19.

Distillation of the phenolic fraction gave 8.7 g. (40%) of unchanged *o*-cresol, b.p. 115–125°/15 mm. The second fraction was 6.5 g. (16% or 28% based on unrecovered starting material) of *2-benzyl-6-methylphenol* (II), b.p. 160–165°/0.75 mm., m.p. 52°, after purification by recrystallization from petroleum ether and sublimation. The ultraviolet spectrum (ethanol solvent) showed a maximum at 274 mμ (ϵ 1.97 × 10^3).

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.76; H, 7.25.

Alkylation of p-cresol. A suspension of the sodium salt of *p*-cresol, prepared from 8.6 g. (0.080 mole) of cresol in 200 ml. of benzene and 1.8 g. (0.080 mole) of sodium heated under reflux for 15 hr. was treated with 29 ml. (0.24 mole) of benzyl bromide under reflux for 6 hr. The product mixture was separated as described above and distillation of the neutral fraction gave 28.3 g. of recovered benzyl bromide

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(10) See L. Hunter, *Progress in Stereochemistry*, Edited by W. Klyne, Academic Press, New York, 1954, Chapter VI; H. C. Brown, D. H. McDaniel and O. Hafliger, *Determination of Organic Structure by Physical Methods*, Edited by E. A. Braude and F. C. Nachod, Academic Press, 1955, pp. 628–31.

(11) S. B. Hendricks, O. R. Wulf, G. E. Hilbert, and U. Liddel, *J. Am. Chem. Soc.*, **58**, 1991 (1936).

(12) See L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co. Ltd., London, 1954, p. 229.

(13) All melting points are corrected. Microanalyses were carried out by Mrs. Maria Stingl. Infrared spectra were determined in 0.1-mm. cells with a Model 21 Perkin-Elmer spectrophotometer by James Brader and Brian Cloonan. Ultraviolet spectra were determined in 1-cm. cells with a Cary Model 14 M spectrophotometer.

(b.p. 80–85°/15 mm.), 2.2 g. (14% or 17% based on unrecovered starting material) of *p*-cresyl benzyl ether (IX),[14] b.p. 98–105°/0.2 mm., m.p. 41–42°, and 0.6 g. (3%) of *benzyl 2-benzyl-4-methylphenyl ether* (VII), b.p. 160–180°/0.3 mm. The ultraviolet spectrum of this compound in cyclohexane shows maxima at 278 mμ (ϵ 2.6 × 10^3) and 287 mμ (ϵ 2.33 × 10^3).

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.60; H, 7.24.

Separation of the phenolic fraction of the reaction mixture by distillation gave unreacted *p*-cresol (1.5 g., 7%), b.p. 92–100°/20 mm., *2-benzyl-4-methylphenol* (VI) (8.1 g., 51% or 62% based on unrecovered starting material), b.p. 122–125°/0.1 mm. and *2,6-dibenzyl-4-methylphenol* (VIII) (1.7 g., 7% or 9% based on unrecovered *p*-cresol), b.p. 170–180°/0.1 mm.

2-Benzyl-4-methylphenol (VI) was a colorless viscous oil. The reported b.p.[4] was 180–182°. The ultraviolet spectrum (cyclohexane) shows an absorption maximum at 282 mμ (ϵ 2.9 × 10^3).

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.89; H, 7.33.

2,6-Dibenzyl-4-methylphenol (VIII) has been reported[4] to have b.p. 250–252°. The ultraviolet spectrum in cyclohexane shows a maximum at 283 mμ (ϵ 2.7 × 10^3).

3-Benzyl-2-hydroxy-5-methylazobenzene (X). To a solution of 1.0 g. (0.0050 mole) of VI and 800 mg. (0.00488 mole) of *N*-nitrosoacetanilide in methanol in an ice bath was added 450 mg. of piperidine with stirring. The solution immediately became a deep red color. After 10 min., it was diluted with water and extracted with ether. After washing of the ether layer with water and drying over magnesium sulfate the ether was removed by distillation to leave 1.3 g. of red oil which was chromatographed on 30 g. of alumina. With 300 ml. of benzene was eluted 800 mg. (57% yield) of crystalline azo compound, m.p. 89°, and further purified by molecular distillation (160°/0.02 mm.).

The ultraviolet spectra showed the following absorption. In ethanol: λ_{max} 333, 395; ϵ 2.9 × 10^4, 1.0 × 10^4. In acetic acid: λ_{max} 332, 397; ϵ 2.5 × 10^4, 8.6 × 10^3. In 0.1*N* sodium hydroxide solution: λ_{max} 335, 497; ϵ 1.1 × 10^4; 1.1 × 10^4. The infrared spectrum of a 10% solution in chloroform showed the following medium-to-large bands other than the usual C—H bending and stretching and the OH stretching which has spread over the region from 3100–2100 cm.$^{-1}$: 1607, 1587, 1493, 1420, 1272, 1140, 871, 687, 697 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.57; H, 5.98; N, 9.08.

3-Benzyl-4-hydroxy-5-methylazobenzene (IV) was prepared by coupling 1 g. (0.00488 mole) of (II) with benzenediazonium acetate prepared from the addition of 450 mg. of piperidine to 800 ml. (0.005) of nitrosoacetanilide in 50 ml. of methanol. After removal of the ether as in the preceding experiment, 1.3 g. of red oil was obtained and chromatographed on 60 g. of alumina. With 300 ml. of a benzene-ethanol (9/1) mixture was eluted 800 mg. (57%) of viscous red oil, molecularly distilled at 175°/0.002 mm., which failed to crystallize.

The ultraviolet spectra showed the following. In ethanol: λ_{max} 255, 352; ϵ 1.4 × 10^4, 2.6 × 10^4. In acetic acid: λ_{max} 351, 284; ϵ 2.3 × 10^4, 1.1 × 10^4. In 0.1*N* sodium hydroxide solution: λ_{max} 465; ϵ 2.9 × 10^4. The infrared spectrum showed, in addition to the usual carbon-hydrogen bending and stretching bands the following: 3605, 1600, 1500, 1295, 1190, 1122, 692, 700 (shoulder) cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.70; H, 6.07; N, 9.32.

3,5-Dimethyl-2-hydroxyazobenzene (XI), m.p. 90°, was prepared by the method of Auwers.[15] The ultraviolet spectra were as follows. In ethanol: λ_{max} 332, 395 mμ; ϵ 2.4 × 10^4, 8.5 × 10^3. In acetic acid: λ_{max} 331, 395, ϵ 2.2 × 10^4, 6.8 × 10^3. In 0.1*N* NaOH: λ_{max} 335, 495; ϵ 8.5 × 10^3, 9.3 × 10^3. The infrared spectrum (10% in chloroform) showed moderate to strong bands at 1590, 1608, 1425, 1280, 1272, 1152, 868, and 687 cm.$^{-1}$ in addition to the usual C—H bending and stretching bands and the general absorption from 3100 to 2100 cm.$^{-1}$ of the hydrogen-bonded OH group.

4-Hydroxy-3,5-dimethylazobenzene (XII), m.p. 94–95°, was prepared according to the directions of Auwers and Markovits.[16] The ultraviolet absorption spectra showed the following. In ethanol: λ_{max} 351, ϵ 2.8 × 10^4. In acetic acid: λ_{max} 351, 280 mμ; ϵ 2.5 × 10^4, 6.9 × 10^3. In 0.1*N* sodium hydroxide solution: λ_{max} 464; ϵ 2.5 × 10^4. The infrared spectrum of a 10% solution in chloroform showed strong to medium bands at 3615, 1600, 1315, 1193, 1122, 1025, 897, and 689 cm.$^{-1}$

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[14] W. Staedel, *Ann.*, **217**, 44 (1883) reports m.p. 41°.

[15] K. Auwers, *Ann.*, **365**, 295 (1909).

[16] K. Auwers and T. Markovits, *Ber.*, **41**, 2340 (1908)

[CONTRIBUTION FROM THE COLLIP MEDICAL RESEARCH LABORATORY AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Steroids and Related Products. IX.[1] The Introduction of the Δ^{11}-Double Bond. I[2]

G. JUST AND CH. R. ENGEL[3]

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A general method for the introduction of the Δ^{11}-double bond, consisting in the dehydrotosylation of a 12α-tosylate with aluminum oxide, is described. Differences in reactivity of the 12α-tosylate toward aluminum oxide in the presence and in the absence of a 17α-methyl substituent, and in the presence and in the absence of a Δ^4-double bond are discussed.

In a recent paper in this series[4] we reported that in the case of 17α-methylated steroids the Δ^{11}-double bond could be introduced easily and in good

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[1] Paper VIII of this series: Ch. R. Engel and R. L. Noble, *Endocrinology*, **61**, 318 (1957).

[2] Some of the results of this work were described in a communication presented before the Division of Medicinal Chemistry at the 126th National Meeting of the AMERICAN CHEMICAL SOCIETY in Dallas, Tex., April 1956; others were included in a paper given before the Division of Organic Chemistry at the annual meeting of the Chemical Institute of Canada, in Vancouver, June 1957.

[3] Correspondence concerning this communication should be addressed to this author.

[4] Ch. R. Engel, K. F. Jennings, and G. Just, *J. Am. Chem. Soc.*, **78**, 6153 (1956).