a solution of 5.25 g. (12.2 mmoles) of 16-ethoxalyl-3-ethylenedioxy-17-hydroxyandrosta-5,16-diene (I)[5b] in 100 ml. of benzene. After the hydrogen evolution had ceased, a solution of 2.96 g. (12.2 mmoles) of dibenzoyl peroxide in benzene was added at 0°. The mixture was allowed to warm to room temperature and stirred for 2.5 days. The resulting mixture was distributed between additional benzene and a 1% potassium hydroxide solution. The benzene solution was washed repeatedly with the alkali until it gave a negative test for an enol with ferric chloride. The dried organic layer was taken to dryness and the residue was treated with 5.0 g. of sodium acetate in 200 ml. of boiling methanol for 1 hr. The solution was taken to near dryness and distributed between methylene chloride and water. The dried organic layer was evaporated, and the residue was recrystallized twice from acetone–petroleum ether to give 1.675 g. of white needles, m.p. 210–215°. The combined mother liquors were taken to dryness, and the residue was chromatographed on silica gel. The solid eluted by benzene–ether (95:5) was recrystallized from acetone–petroleum ether to give 0.494 g. (40% total yield) of white needles, m.p. 210–215°. Material from a similar experiment had m.p. 210–215°; $[\alpha]^{25}D$ +35°; λ_{max} 230 mμ (ε 15,500); λ_{max} 5.70, 5.80, 6.22, 6.30, 7.80, 8.97, 13.94 μ; positive blue tetrazolium test.

Anal. Calcd. for $C_{23}H_{34}O_5$ (450.55): C, 74.64; H, 7.61. Found: C, 74.45; H, 7.72.

3-Ethylenedioxy-16β,17β-dihydroxyandrost-5-ene (III).—To a magnetically stirred slurry of 0.760 g. (20 mmoles) of lithium aluminum hydride in 25 ml. of ether was added dropwise a solution of 0.900 g. (2.0 mmoles) of 16β-benzoyloxy-3-ethylenedioxyandrost-5-en-17-one (II) in 30 ml. of benzene. The mixture was heated at reflux temperature for 1 hr. and allowed to stand at room temperature for 1.5 hr. The excess hydride was destroyed by addition of ethyl acetate, and the mixture was treated with a 5% hydrochloric acid solution and extracted with methylene chloride. The dried extract was evaporated, and the residue was triturated with ether and filtered to give 0.575 g. (83% yield) of white crystals, m.p. 228–231°. A sample was recrystallized twice from acetone–petroleum ether to give white crystals, m.p. 226–228°; no significant absorption in the ultraviolet at 20 γ/ml.; λ_{max} 2.88, 9.09 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$ (348.47): C, 72.38; H, 9.26. Found: C, 71.59, 71.18; H, 9.13, 9.10.

16β-Hydroxytestosterone (IV).—A solution of 0.500 g. (1.44 mmoles) of 3-ethylenedioxy-16β,17β-dihydroxyandrost-5-ene (V) in 20 ml. of methanol containing 1 ml. of 8% sulfuric acid solution was heated at reflux temperature for 2 hr. The solution was diluted with 30 ml. of water and evaporated until solid separated. The mixture was extracted with methylene chloride, and the combined extracts were washed with sodium bicarbonate solution, dried, and taken to dryness. The residue was crystallized from acetone–petroleum ether to give 0.283 g. of long needles, m.p. 182–184°. Concentration of the mother liquor gave an additional 39 mg. of needles. Material from a similar experiment was obtained as white needles, m.p. 188–189°; a mixture with 16α-hydroxytestosterone melted at 160–168°.[15] The material had $[\alpha]^{25}D$ +105°, +93° (methanol); λ_{max} 240 mμ (ε 15,800); λ_{max} 3.02, 6.08, 6.20 μ. Reported values are m.p. 172–173°,[10a] 179–182°,[10b] and 183.5–185.5°[10c] $[\alpha]D$ +101°, +94 (dioxane),[10b] +103°.[10c]

Anal. Calcd. for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27. Found: C, 74.52; H, 9.69.

This material formed a diacetate, obtained from methanol as white needles, m.p. 205–206°; $[\alpha]^{25}D$ +90°; λ_{max} 240 mμ (ε 16,500); λ_{max} 5.75, 5.97, 6.18, 7.95, 8.10 μ. (Reported values are m.p. 201–202.5°,[10b] 204–205.5°;[10c] $[\alpha]^{25}D$ +88°,[10b] +90°[10c].)

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.31; H, 8.42.

On treatment with acetone–perchloric acid the diol gave an acetonide, obtained from petroleum ether as needles, m.p. 189–191°; $[\alpha]^{25}D$ +120°; λ_{max} 240 mμ (ε 13,600); λ_{max} 6.00, 6.19, 7.29, 7.34, 9.46, 11.58 μ. Reported values are m.p. 183–184°,[10a] 185–187°,[10b] and 183.5–187°.[10c]

Anal. Calcd. for $C_{22}H_{32}O_3$ (344.48): C, 76.70; H, 9.36. Found: C, 76.83; H, 9.42.

2α-Benzoyloxy-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione (V).—A solution of 224 mg. (2.0 mmoles) of potassium *t*-butoxide and 977 mg. (2.0 mmoles) of 3-hydroxy-2-methoxalyl-17α,20;20,21-bismethylenedioxypregn-2,4-dien-11-one[12] was treated with a solution of 484 mg. (2.0 mmoles) of dibenzoyl peroxide in 25 ml. of benzene. The resulting mixture was stirred at room temperature for 23 hr. and then distributed between methylene chloride and water. The dried organic solution was taken to dryness, and the residue was treated with 1.00 g. of potassium acetate in 25 ml. of boiling methanol for 1 hr. The solution was taken to dryness; the product was isolated with methylene chloride and chromatographed on a silica gel column (1.2 × 16.5 cm.). Elution with benzene–ether (9:1) gave in fractions 3 and 4 (100 ml. each) a solid that was rechromatographed on a silica gel column (1.0 × 17 cm.). Elution with benzene–ether (9:1), 50 ml. fractions being collected, gave in fraction 2 material which was recrystallized from methanol to give 87 mg. (8% yield) of white needles, m.p. 203–205°; $[\alpha]^{25}D$ +74°; λ_{max} 233 mμ (ε 30,500); λ_{max} 5.85, 6.15, 6.22, 6.29, 7.85, 8.88, 9.10, 14.02 μ; positive blue tetrazolium test.

Anal. Calcd. for $C_{30}H_{34}O_8$ (522.57): C, 68.95; H, 6.56. Found: C, 68.50; H, 6.37.

Acknowledgment.—We are indebted to Mr. L. Brancone and his staff for the microanalyses and to Mr. W. Fulmor and his staff for the spectral and polarimetric data.

(14) Melting points were taken in an open capillary tube and are uncorrected values. The ultraviolet spectra were determined in methanol on a Cary recording spectrophotometer and the infrared spectra (pressed potassium bromide disks) were carried out with a Perkin–Elmer spectrophotometer (Model 21). Polarimetric data were obtained in chloroform solution unless stated otherwise. All evaporations were carried out under reduced pressure, and the petroleum ether used was that fraction boiling at 60–70°.

(15) (a) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 297 (1956); (b) We are indebted to Dr. C. E. Holmlund of these laboratories for a specimen of this material.

Aza-Aromatic Substitution. II. Debromination and Isomerization of 3-Bromoquinoline at Higher Temperatures

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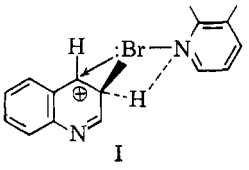
In rationalizing the selective and facile bromination of quinoline at C-3 by the decomposition of the 1:1 quinoline–bromine complex, it was postulated that C-3 was attacked in preference to C-6 because of the favorable circumstances for a bridged bromonium ion transition state at C-3 (I).[1] By the principle of microscopic reversibility

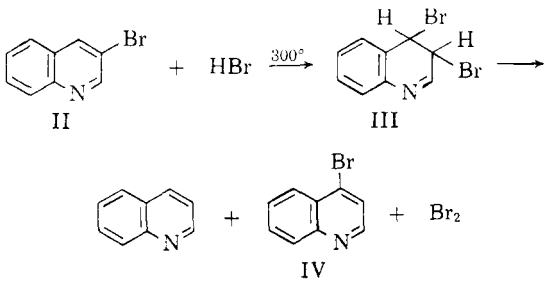
(1) Paper I of this series: J. J. Eisch, *J. Org. Chem.*, **27**, 1318 (1962).



I

it should follow that the reverse polar process, debromination, should also occur more readily at C-3 than at C-6; the bromonium ion loss would be facilitated by the same type of transition state stabilization (I). To test the validity of this hypothesis, the hydrobromide salts of 3-bromoquinoline and 6-bromoquinoline were heated individually at 300° under a nitrogen atmosphere. Since both salts are known to dissociate partially upon heating,[2] these systems were good models for studying the possible reversibility of bromination.

The heating of 3-bromoquinoline hydrobromide at 300° did indeed effect debromination, as evidenced by the isolation of quinoline from the product and by the detection of free bromine in the reaction mixture. The latter point was demonstrated by conducting the decomposition in the presence of phenol and isolating *p*-bromophenol as its phenoxyacetic acid derivative. Most striking was the fact that the recovered 3-bromoquinoline from shorter contact times contained considerable amounts of 4-bromoquinoline (IV). The formation of the 4-isomer was verified by infrared spectral comparison with an authentic sample and the facile hydrolysis of pyrolysis product to yield 4-hydroxyquinoline.[3] No other monobromoquinolines were present in significant amounts. Longer reaction times led to a bromoquinoline fraction composed principally of 4-bromoquinoline and smaller amounts of the 3- and 5-isomers. In addition, a considerable portion of polybromoquinolines was formed; however, only 3,4-dibromoquinoline (V) could be identified with some certainty. Since free bromine was present during the reaction, V could most simply arise from the selective bromination of IV at C-3.[1] However, the formation of IV as the principal product in the bromination of quinolinium bromide[4] or of quinoline itself[1,5] would not be consistent with experimental findings. On the other hand, both the debromination and isomerization of 3-



II III IV

bromoquinoline find a mutual explanation in the formation of I either by the addition of hydrogen bromide to the 3,4-bond of II to produce III transitorily with subsequent ionization of either C-Br bond or by the direct protonation of II. Thereafter, the loss of the bromonium ion (debromination) or its transfer to C-4 with proton loss (isomerization) would lead to the observed products. As is consistent with the electronic factors stabilizing I,[1] 6-bromoquinoline hydrobromide underwent no detectable debromination or rearrangement under the same conditions. In 6-bromoquinoline C-5 cannot proffer a similarly low charge density to stabilize a transition state analogous to I.

Finally, it has been suggested that the bromination of pyridine and quinoline at 300°, leading to the 3-isomer,[5] involves electrophilic substitution, while the formation of the 2-isomer as the major product at 500° indicates the dominance of free radical substitution.[6] The foregoing study demonstrates the reversibility of bromination at C-3 at 300° and hence indicates that the switch in the orientation of bromination between 300 and 500° need not betoken a change in mechanism. The predominance of the 2-isomer at 500° may simply reflect the instability of other isomers at this temperature. Both substitution processes might still involve the same mechanism, be it a polar or free radical pathway.

Experimental

Pyrolysis of 3-Bromoquinoline Hydrobromide.—(a) Pure 3-bromoquinoline[1] in anhydrous ether reacted with dry hydrogen bromide gas to precipitate 3-bromoquinoline hydrobromide. After collection by filtration, washing with anhydrous ether, and air drying, the solid was triturated to a fine powder and heated at 50° under 1-mm. pressure for 2 hr.

Under a nitrogen atmosphere a 200-ml. flask containing 48.0 g. (0.171 mole) of 3-bromoquinoline hydrobromide was immersed in an oil bath heated to 300° and the system was maintained at 300 ± 2° for 90 min. During the reaction period hydrogen bromide gas and bromine vapor were evolved (litmus and iodide–starch indicators), as the salt became a dark, molten mass. The cooled reaction product was made basic with ammonium hydroxide and the liberated organic bases were extracted with ether. Drying and distillation of the ether extract gave a residue which was fractionally distilled through a 30-cm., glass helices-filled column.

(2) (a) A. Claus and F. Collischonn, *Ber.*, **19**, 2763 (1886), report that 3-bromoquinoline hydrobromide yields 3-bromoquinoline and hydrogen bromide upon rapid heating; (b) A. Claus and V. Tornier, *ibid.*, **20**, 2892 (1887), mention that 6-bromoquinoline hydrobromide dissociates partially under 100°.

(3) A. Claus and H. Howitz, *J. prakt. Chem.*, **50**, 232 (1894).

(4) P. B. D. De La Mare, M. Kiamud-Din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960), found only 5- and 8-bromoquinolines in the electrophilic bromination of the quinolinium ion.

(5) H. E. Jansen and J. P. Wibaut, *Rec. trav. chim.*, **56**, 699 (1937), isolated only 3-bromoquinoline in the vapor phase bromination of quinoline. In unpublished studies we have repeated this work and found the 3- and 8-isomers, with only traces of the 4-isomer. However, compared with the debromination process (the pyrolysis of 3-bromoquinoline hydrobromide) vapor phase bromination involves relatively short contact times at 300°.

(6) *Cf.* G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1955, p. 485.

The fractions collected at 20-mm. pressure were the following: (1) 118–120°, 7.1 g., $n^{22}D$ 1.6266; (2) 120–135°, 1.2 g., $n^{22}D$ 1.6325; (3) 136–148°, 0.6 g., $n^{22}D$ 1.6572; (4) 149–152°, 3.4 g., $n^{22}D$ 1.6612; (5) 153–157°, 3.5 g., $n^{22}D$ 1.6620; (6) 157–158°, 1.5 g., $n^{22}D$ 1.6625. The residue (12.4 g.) was extracted with three portions of hot petroleum ether (b.p. 30–60°) to yield upon evaporation of the solvent semisolid crops (fractions 7, 8, and 9). Fractions 1 and 2 were shown to be mainly quinoline (38%) by infrared spectral comparison with an authentic sample and by the preparation of a picrate, m.p. 202–204°. Admixture with authentic quinoline picrate (m.p. 202–204°) gave no depression in melting point. By comparison with the authentic infrared spectra of all of the known bromoquinolines[1] fractions 3 and 4 were shown to contain 3-bromoquinoline and a new substance, contaminated with small amounts of quinoline. In a similar fashion, fractions 5 and 6 were shown to contain 3-bromoquinoline and the same unknown component in approximately equal amounts. By careful study of the infrared spectra of these fractions and by reference to the spectra of the known bromoquinolines[1] all the new infrared bands, not ascribable to the presence of 3-bromoquinoline, occurred only in the spectrum of authentic 4-bromoquinoline: 650, 758, 805, 834, 868, 962, 1050, 1280, 1370, and 1550 cm.$^{-1}$. Characteristic, intense infrared bands of the 2-, 5-, 6-, 7-, and 8-bromoquinolines were completely absent in the infrared spectra of fractions 1–6; this rules out their occurrence in these pyrolysis products in other than minute quantities (*cf. infra*). Fraction 7 possessed an infrared spectrum resembling a mixture of 3- and 4-bromoquinolines, together with new bands at 660, 810, 910, 960 (broadening), 1100, 1165, 1345, and 1490 cm.$^{-1}$. Again, all these new bands were found in the infrared spectrum of authentic 3,4-dibromoquinoline. Fractions 8 and 9 displayed infrared spectra identical with that of fraction 7, except that weak, unassigned bands occurred at 702, 830, and 1670 cm.$^{-1}$. The residue from the petroleum ether extractions consisted of an intractable mixture of polybromoquinolines melting over the range 75–200°, whose infrared spectrum had no definite OH, NH or C=O absorptions but pronounced, broad absorptions in the 950–975-cm.$^{-1}$ region (vicinal trisubstituted benzenoid or pyridinoid system).

(b) In similar runs of 0.20-mole size, where the heating period was extended over 2–3 hr., the isolated bromoquinoline was largely 4-bromoquinoline, contaminated with small amounts of 3- and 5-bromoquinolines. Thus upon distillation of the crude product, after a forerun of quinoline, the main fraction was collected at 140–145° (7 mm.), $n^{22}D$ 1.6620. The infrared spectrum was superposable with that of 4-bromoquinoline, except for weak bands indicative of small amounts of recovered 3-bromoquinoline and weak bands at 950, 1035, and 1215 cm.$^{-1}$, characteristic of 5-bromoquinoline. This fraction was heated at reflux with 12 *N* sulfuric acid for 12 hr. The solution was made basic with sodium hydroxide solution and extracted with ether to remove the unchanged bromoquinolines. The aqueous layer was brought to neutrality with sulfuric acid and then evaporated to dryness. Extraction of the solid residue with dry acetone and evaporation of the acetone extract left a solid residue. This solid was shown to be 4-hydroxyquinoline by the comparison of its infrared spectrum with that of an authentic sample.

(c) The presence of free bromine in the pyrolysis was verified by conducting the reaction in the presence of phenol. Over a 30-min. period an intimately mixed paste of 27.5 g. (0.095 mole) of 3-bromoquinoline hydrobromide and 9.4 g. (0.10 mole) of pure phenol was heated up to 300° under a nitrogen atmosphere. The temperature was maintained at 300 ± 5° for 1 hr. under reflux of the phenol. Thereafter the excess phenol was distilled at atmospheric pressure. Treatment of the cooled residue with sodium hydroxide solution and extraction with ether yielded an aqueous layer of sodium phenoxides. The latter solution was treated with chloroacetic acid according to published directions[7] to yield 0.10 g. of the crude phenoxyacetic acid, melting over the range 140–150°. Recrystallized thrice from hot water, the product formed colorless, flat needles, m.p. 157–159°. Mixture melting point and infrared spectral comparison with an authentic sample (m.p. 158–159°) showed the product to be *p*-bromophenoxyacetic acid.

The ether layer from the pyrolysis work-up was evaporated and the residual oil was extracted with hot, dilute tartaric acid solution. Treatment of the tartaric acid extracts with ammonium hydroxide and isolation by ether extraction provided 4.0 g. (32%) of quinoline, $n^{22}D$ 1.6300; picrate, m.p. 201–203°.

Pyrolysis of 6-Bromoquinoline Hydrobromide.—In an analogous fashion 15.7 g. (0.054 mole) of 6-bromoquinoline hydrobromide was heated at 300 ± 2° for 90 min. under a nitrogen atmosphere. The initially cream-colored solid gradually became a dark melt as hydrogen bromide gas was evolved. Usual work-up and distillation gave 10.0 g. (89% recovery) of pale yellow oil, b.p.$_{21}$ 167–168°, $n^{25}D$ 1.6599, with no forerun. By examination of its infrared spectrum the distillate was shown to be pure 6-bromoquinoline; no bands characteristic of quinoline or any other bromoquinoline were present.

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1960, p. 264.

The Chemistry of Cyclic Hydrazides.[1] VIII. The Preparation of Substituted N-Aminomaleimides and Their Conversion to N-Substituted Maleic Hydrazides[2]

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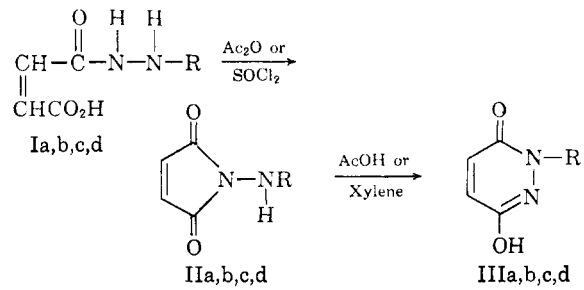
In 1958, we reported a novel preparation of substituted N-aminomaleimides and their subsequent rearrangement to N-substituted maleic hydrazides. This work deals with the preparation of new aryl and alkyl derivatives of N-aminomaleimides and the study of the electrical effect of substituents, situated on the amino nitrogen, on



Ia,b,c,d IIa,b,c,d IIIa,b,c,d

a. R = —$COCH_3$; b. R = —$SO_2C_6H_5$; c. R = —$C_6H_3(NO_2)_2$-*m*; d. R = —C_6H_5.

(1) Previous pertinent paper in this series, H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

(2) From the M.S. thesis of John P. Asunskis, Purdue University, August, 1961.