tion spectra showed no change on further chromatographing; $\lambda_{max(\mu)}^{film}$ 2.95 (OH), 3.45 (CH), 6.10, 6.20 (C=O, C=C), 7.25, 7.40 (CH_3), 7.85 (=C—O—C), 8.70 (=C—OH).

Anal. Calcd. for $C_{27}H_{44}O_4$ (chroman ring closed): mol. wt., 432; C, 75.0; H, 10.3. For $C_{28}H_{48}O_4$ (chroman ring open): mol. wt., 448: C, 75.0; H, 10.8. Found: C, 74 6; H, 10.4; mol. wt., Rast, 967 (dimer); equiv. wt. from potentiometric titration, 477–510.

Synthesis of Tetramethyl-6-hydroxychromans.—The synthetic scheme of Smith[5] was followed for the synthesis of the model 6-hydroxychromans. 2,3-Dimethyl-1,4-hydroquinone was synthesized by the method of Emerson[7] *via* dichromate oxidation of *o*-xylidine sulfate followed by reduction of the quinone with zinc and acetic acid.

2,2,5,7-Tetramethyl-6-hydroxychroman (IX).—Condensation of 2,6-dimethyl-1,4-hydroquinone with isoprene by refluxing for 2 hours in glacial acetic acid with zinc chloride[5] as catalyst yielded an oil after addition of water and extraction with petroleum ether (b.p. 30–60°). Unreacted hydroquinone was removed by extraction of the petroleum ether solution with 5% aqueous sodium hydroxide. Extraction with Claisen alkali removed the desired chroman (IX) from the petroleum ether solution.

The crude oily chroman was sublimed at 60° and 1 min. to yield a colorless oil which crystallized upon addition of petroleum ether (b.p. 30–60°) to yield IX in 9% yield, m.p. 92.5–93.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.80, 2.90 (OH), 7.25, 7.40 (CH_3), 8.12 (=C—O—C), 8.55 (=C—OH).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.80. Found: C, 75.7; H, 9.00.

2,2,5,8-Tetramethyl-6-hydroxychroman (X).—Condensation of 2,5-dimethyl-1,4-hydroquinone with isoprene in acetic acid, using zinc chloride as catalyst, gave a very low (<5%) yield of X, m.p. 77–78° from petroleum ether (b.p. 30–60°). (An equal amount of the double chroman XI, m.p. 193–196°, was also produced.) The insolubility of the hydroquinone in acetic acid hampers the reaction, most of it being recovered unchanged; (X) $\lambda_{max(\mu)}^{Nujol}$ 3.05 (OH), 6.21, 6.68 (aryl), 7.20, 7.30 (CH_3), 8.00 (=C—O—C), 8.55 (=C—OH); (XI) $\lambda_{max(\mu)}^{Nujol}$ 7.25, 7.30 (CH_3), 7.90, 8.20 (=C—O—C).

Anal. Calcd. for $C_{13}H_{18}O_2$ (X): C, 75.7; H, 8.80. Found: C, 75.7; H, 8.73. Calcd. for $C_{18}H_{26}O_2$ (XI): C, 78.8; H, 9.55. Found: C, 78.5; H, 9.32.

Oxidation of VII and IX with Ferric Chloride.—Ferric chloride hexahydrate (16 g.) was added to a 25-ml. volume of methanol to which had been added 800 mg. of VII or IX. The solution was refluxed for 3 hours, cold water was added, and the oxidation products were ether extracted; the ether extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The brown-red oil was chromatographed on a zinc carbonate–Celite column with the purple band remaining at the top of the column and an orange band moving ahead upon petroleum ether elution. The purple band was removed from the column with methanol containing 0.25 wt. % potassium hydroxide and acidified to a yellow color with 5% hydrochloric acid. The hydroxyquinone XII was extracted with diethyl ether after adding water to the methanol solution. Concentration of the ether extracts after drying yielded crude XII. Recrystallization from petroleum ether (b.p. 30–60°) yielded an analytical sample of XII, m.p. 142–143.5°, orange crystals; John[6] reported m.p. 140° (same compound obtained from oxidation of either VII or IX); $\lambda_{max(\mu)}^{Nujol}$ 3.00 (OH), 6.05, 6.20 (C=O, C=C), 7.25, 7.40 (CH_3), 7.75 (=C—O—C), 8.66 (=C—OH). The ultraviolet absorption maximum in methanol was at 296 mμ with ε 18,200; John[6] reported a maximum at 298 mμ with ε 20,000.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.8; H, 6.35. Found: C, 64.7; H, 6.36.

Acknowledgments.—The authors wish to thank Dr. J. Shoolery of Varian Associates for interpretation of the nuclear magnetic resonance spectra and to thank Dr. Peter Lim of the Institute's Biological Sciences Department for interpretation of the infrared absorption spectra. We are also indebted to the Institute's Physical Sciences Divisional Research Committee for partial support of this work.

(7) O. H. Emerson and L. I. Smith, THIS JOURNAL, **62**, 141 (1940).

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. VII. The Neber–Bossel Synthesis[1,2]

BY HENRY E. BAUMGARTEN AND PAUL L. CREGER[3]

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Although the cyclization of *o*-hydrazinomandelic acid is known to yield 3-cinnolinol (3-hydroxycinnoline) (the Neber-Bossel synthesis), the cyclization of α-substituted *o*-hydrazinomandelic acids may yield either the corresponding 4-substituted 3-cinnolinol or the 3-substituted 1-aminodioxindole.

At present 3-cinnolinol (3-hydroxycinnoline, Va) is best synthesized by a sequence consisting of the diazotization of *o*-aminomandelic acid (IIIa), reduction of the diazonium salt with stannous chloride and hydrochloric acid and cyclization of the resultant *o*-hydrazinomandelic acid (IVa) by heating in aqueous acid. The original work on this synthesis was published only in dissertation form,[4] and all of the available knowledge of this method is due to a study by Alford and Schofield,[5] who have labeled the procedure the Neber–Bossel synthesis.

(1) Paper VI. THIS JOURNAL, **82**, 3977 (1960).

(2) This work was initiated with the support of National Science Foundation grant, G-1090, and completed with the support of U. S. Public Health Service grant, CY-3090, and a grant from the University of Nebraska Research Council. This communication is abstracted from the Ph.D. thesis (June, 1957) of P.L.C.

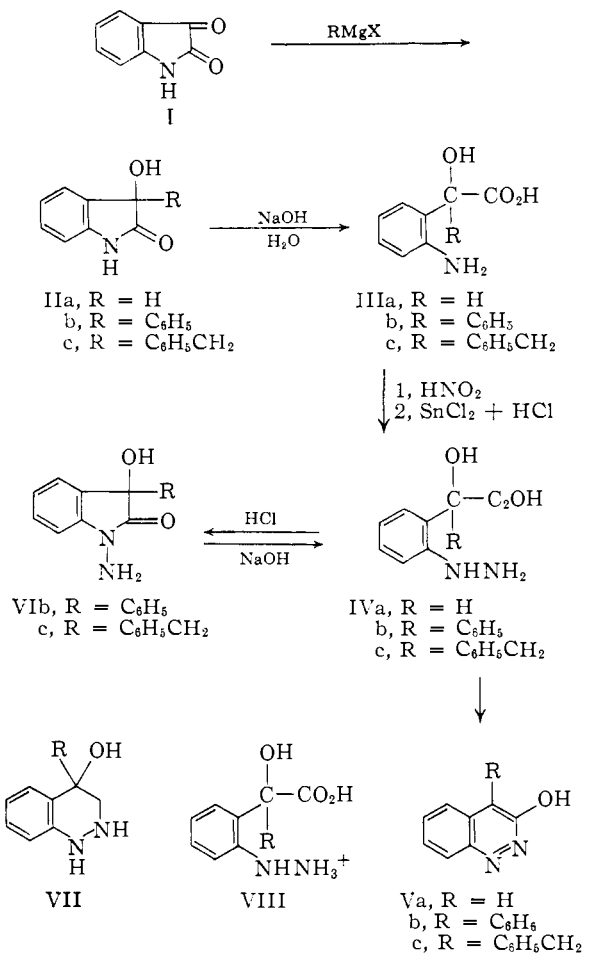
(3) Eastman Kodak Co. Fellow, 1955-1956.

(4) G. Bossel, Inaug. Diss. Tubingen, 1925; *Chem. Zentr.*, **100. II**, 3015 (1929).

(5) E. J. Alford and K. Schofield, *J. Chem. Soc.*, 2012 (1952).

In their experiments Alford and Schofield prepared IIIa by converting *o*-nitrobenzaldehyde into the corresponding cyanohydrin, *o*-nitromandelonitrile, followed by hydrolysis of the nitrile function and reduction of the nitro group. Although they were able to realize a 59% yield of Va (based on *o*-nitrobenzaldehyde), the attempted application of their multi-step version of the Neber–Bossel procedure to the synthesis of 6-chloro- and 6-methoxy-3-cinnolinol gave only low yields of the expected products. The present communication describes an extension of this synthesis to 3-cinnolinols having a substituent other than hydrogen in the 4-position.

Although *o*-nitroaryl ketones might be the logical starting materials for the objective at hand, the difficulty with which such materials are prepared caused us to direct our attention to the use of isatin (I) for this purpose. The reaction sequence is



shown in the transformations, I → VI. The reaction of isatin (I) with Grignard reagents has been described by several workers,[6] most of whom have followed the procedure of Kohn[6a] or Kohn and Ostersetzer.[6b] By a modification of this procedure, 3-phenyldioxindole (IIb) was prepared in 55% yield from the reaction of I with phenylmagnesium bromide and 3-benzyldioxindole (IIc) in 48–56% yield from the reaction of I with benzylmagnesium chloride.

Despite an early discouraging report,[7] several recent investigators[8–10] have been able to bring about the successful hydrolytic cleavage of the dioxindole ring in alkaline solution to form salts of various 2-aminomandelic acids. Thus, in the present work, IIb was heated with aqueous potassium hydroxide and the resulting solution (presumably containing the potassium salt of IIIb) was diazotized without attempting to isolate IIIb. During the diazotization some IIb (8–10%) was reformed. The presence of a diazonium salt in the solution was demonstrated in the usual manner by reaction with β-naphthol. Reduction of the diazonium salt at 0° with stannous chloride and hydrochloric acid gave a tin complex[11] which on warming to 5–10° underwent a considerable change in appearance, giving a substantially tin-free product, identified as 1-amino-3-phenyldioxindole (VIb) in 42–45% yield (35–38% conversion, based on IIb).

Application of this same sequence to IIc gave a 40% yield (20–25% conversion) of 1-amino-3-benzylidioxindole (VIc), the recovered IIc (40–50%) being much greater in this second example.

The structures of the products (VI rather than V or VII) were established by consideration of the elementary analyses, ultraviolet and infrared spectra. The analyses indicated that the products might be VI or VII or hydrates of V; however, the products were colorless whereas all known simple derivatives of V are bright yellow (as are their hydrates). Furthermore, the infrared and ultraviolet spectra of the products differed markedly from those of the known derivatives of V. The choice between VI and VII was not so unequivocal. The rationale employed was essentially the same as that used to establish the structure of 1-aminoöxindole.[1] Thus, the location and contour of the infrared absorption bands in the ν(N–H) region for VIb and VIc were essentially the same as for the corresponding bands for 1-aminoöxindole and α-acetylphenylhydrazine except for an additional band due to the ν(O–H) vibration in the spectra of VIb and VIc. Furthermore, the positions of the ν(C=O) bands in the spectra of VIb and VIc were in the correct locations for 5-ring lactams when the proper allowance was made for the frequency-lowering effect of the N-amino group.[1] These data are summarized in Table I. Some pertinent ultraviolet spectral data are recorded in Table II.

TABLE I

INFRARED SPECTRA[a]

Compound	Frequency, cm.⁻¹ ν(C=O) region[b]	ν(N–H), (O–H) region[c]
3-Phenyldioxindole	1732s	3551m; 3432s
1-Amino-3-phenyldioxindole	1717s	3590sh, 3549s; 3410sh, 3350s, 3291w
1-Methyl-3-phenyldioxindole	1724s	3550m
4-Phenyl-3-cinnolinol	1638s	3365m
1-Benzalamino-3-phenyldioxindole	1720s	3560m
3-Benzyldioxindole	1730s	3554m; 3435s
1-Amino-3-benzyldioxindole	1718s	3593sh, 3556s; 3406sh, 3350s, 3293w
4-Benzyl-3-cinnolinol	1636s	3382m

[a] Run using Perkin–Elmer model 21 double beam spectrometer with chloroform solution, the chloroform being freed from alcohol just prior to use by technique described previously.[1] [b] Run with NaCl prism; concentration was 6.0 mg./ml. in 0.1- and 1.0-mm. cells; relative intensity designations refer to entire NaCl spectrum. [c] All compounds with —N–H run with LiF prism; concentration was 0.005 *M* in 5-mm. cell for —N–H compounds and 0.025 *M* in 5-mm. cell for —N–NH_2 compounds; compounds with no —N–H run with NaCl prism. Relative intensity designations refer only to peaks in the ν(N–H), (O–H) region; where both ν(O–H) and ν(N–H) peaks appear in the spectrum, the ν(O–H) peak is listed to the left of the semicolon.

When VIb was hydrolyzed in hot, dilute aqueous base and the resultant solution (presumably con-

(6) (a) M. Kohn, *Monatsh.*, **31**, 747 (1911); (b) M. Kohn and A. Ostersetzer, *ibid.*, **34**, 789 (1913).

(7) C. Marshalk, *Ber.*, **46**, 583 (1913).

(8) Halberkann, *ibid.*, **54**, 3079 (1921).

(9) W. Steinkopf and W. Hanske, *Ann.*, **541**, 238 (1939).

(10) *Cf.* purification procedures in ref. 6, although no proof of ring opening on treatment with alkali was offered.

(11) The nature of this complex was not determined other than to demonstrate the presence of stannic ions.

TABLE II

ULTRAVIOLET SPECTRA[a]

Compound	λ_{max}, mμ	log ϵ_{max}
Acetanilide	242, 281	4.15, 2.78
α-Acetylphenylhydrazine	240	3.75
β-Acetylphenylhydrazine	236, 282	4.04, 3.20
Oxindole	248, 279	3.98, 3.17
1-Aminoöxindole	254, 282*	3.97, 3.30
1-Methyloxindole	252, 280*	3.99, 3.20
3,4-Dihydro-2(1H)-quinolinone	249, 280*	4.09, 3.30
1-Amino-3,4-dihydro-2(1H)-quinolinone	257	3.98
3-Phenyldioxindole	253, 293	3.83, 3.20
1-Amino-3-phenyldioxindole	263, 306*	3.83, 3.28
3-Benzyldioxindole	252, 288	3.79, 3.15
1-Amino-3-benzyldioxindole	261, 300*	3.79, 3.26

[a] These spectra were run using a Cary model 11 recording spectrophotometer and 10^{-4} *M* solutions in 95% ethanol. Most of the spectra consisted of two peaks, the smaller of which was not always well-resolved, appearing as a shoulder on the larger peak. Poorly resolved peaks are indicated by an asterisk (*).

taining a salt of IVb) was carefully neutralized, 4-phenyl-3-cinnolinol (Vb) was formed in 46% yield. The remainder of the product was regenerated VIb. Similarly, VIc gave 4-benzyl-3-cinnolinol (Vc), but in only 10–30% yield, accompanied by a substantial recovery of VIc. The assigned structures were confirmed by elementary analyses and infrared and ultraviolet spectra. The easy formation of the cinnoline derivatives afforded further confirmation of the identity of VIb and VIc.

The formation of V and VI but not VII indicates, as might be expected, that intermediates such as VII probably are not stable. However, it might appear that V, with its greater resonance stabilization, would be the preferred product. The formation of the 5-ring in preference to the 6-ring may be attributed in the present examples to both steric and electrical effects. In concentrated hydrochloric acid solution such as that used in reducing the aromatic diazonium chlorides, the resulting hydrazino group would be converted largely into the hydrazonium ion VIII, the more basic nitrogen being protonated. Little free IV would be present. The terminal nitrogen (N-β) would lose its nucleophilic character, permitting the normally more weakly nucleophilic (N-α)-nitrogen to attack the carbonyl moiety of the carboxyl group to form VI. In the subsequent hydrolysis and careful neutralization a sufficient concentration of free IV must be present to permit some cyclization involving the (N-β)-nitrogen. The regeneration of VI can be attributed to incomplete cleavage of the 1-aminodioxindole ring, to the formation of a zwitterion of IV (presumably a β-protonated species) in equilibrium with IV or possibly to steric factors such as the smaller number of atoms that need to be in position to promote ring closure to VI (frequency factor). The facile ring closure of IVb and IVc compared with the more difficult cyclization[1] of *o*-hydrazinophenylacetic acid may be another example of the effect of substituents upon the ease of formation of small rings.[12]

(12) E. L. Eliel in M. S. Newman's, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 117–120.

These results could, by analogy, explain the low yields obtained by Alford and Schofield[5] in the synthesis of 6-chloro- and 6-methoxy-3-cinnolinol. Inasmuch as other work in this Laboratory had already indicated that the 6-chloro derivative had been incorrectly characterized by Alford and Schofield, their preparation of this compound was repeated. Our results apparently were identical with those of Alford and Schofield with respect to yields[13] and physical constants; however, the infrared spectrum of the product indicated it to be a mixture of 6-chloro-3-cinnolinol with some unknown substance which did not appear to be a derivative of VI. This result may indicate that derivatives of VI with R = H, which must have steric requirements different from those of IVa and IVb, do not form under the conditions of the Neber–Bossel synthesis or that such derivatives are less stable than those obtained in the present work.

A number of attempts have been made to synthesize IVa (and thence Va) by the reduction of I to IIa with sodium hydrosulfite followed by hydrolytic cleavage of the ring, diazotization and reduction or by hydrolytic cleavage of I followed by reduction with sodium borohydride or hydrogen over platinum (to form IIIa), diazotization and reduction. Thus far these experiments have been unsuccessful.

Experimental[14]

3-Phenyldioxindole (IIb).—A flask equipped with a dropping funnel and a Soxhlet extractor (modified for constant return of the extract) and protected by a drying tube was charged with 5.0 g. (3 × 0.068 mole) of magnesium turnings and 50 ml. of dry ether. A crystal of iodine was introduced, then a few drops of a solution of 32.0 g. (3 × 0.068 mole) of bromobenzene in 50 ml. of dry ether was added, and, when the reaction had begun, the remainder of the bromobenzene was added at such a rate (30–45 min. required) so as to maintain moderate reflux.

When all of the bromobenzene had been added, the ether solution was heated to reflux for an additional 15 min., then 300 ml. of dry benzene was introduced through the dropping funnel and the Soxhlet thimble was charged with 10.0 g. (0.068 mole) of isatin. The benzene solution was heated under reflux for 24 hr., which was sufficient time for nearly all of the isatin to dissolve and react. However, a small amount of isatin was recovered from the thimble in nearly every run.

To the mixture was added 100 g. of 10% sulfuric acid, and the mixture was steam distilled to remove the biphenyl, 1.5–2 l. of distillate being collected. After the residue in the still pot had been cooled to 10–15° in the ice-bath, the solid formed was collected and digested with 200 g. of 15% sodium hydroxide. After the basic solution had been treated with charcoal and filtered, the *p*H of the solution was adjusted to 2 by addition of 6 *N* sulfuric acid. The solid formed was collected and washed liberally with water to remove the sodium sulfate which separated with the product. The 3-phenyldioxindole remaining was recrystallized (charcoal) from 75 ml. of 50% ethanol or 50% acetic acid (with prolonged cooling in the refrigerator), giving 8.5 g. (55%) based on isatin consumed of nearly colorless needles, m.p. 209–211° dec. Repeated recrystallization from 50% ethanol raised the m.p. to 211.5–214° dec. (lit.[6a] m.p. 213°).

This procedure was found to be much more attractive from a manipulative standpoint and to give better yields than that of Kohn[6a] (who did not report a yield; however, in our hands his procedure gave a 19% yield).

(13) A fortuitous aversion to dish-washing led to the observation that the crude yield could be very substantially increased by allowing the final reaction mixture (or its filtrate) to stand at room temperature for about one week.

(14) Melting points are corrected; boiling points are not. Analyses by Micro-Tech Laboratories, Skokie, Ill.

1-Methyl-3-phenyldioxindole was prepared from 0.05 mole of 1-methylisatin essentially by the procedure of Kohn and Ostersetzer.[6c] After purification by dissolution in warm 2 *N* sodium hydroxide solution (on the steam-bath in *ca.* 15 min.), reacidification with acetic acid and recrystallization from 50% acetic acid, the yield of nearly colorless plates was 2.5 g. (21%), m.p. 140–141° (lit.[6c] m.p. 139°).

3-Benzyldioxindole (IIc) was prepared by the procedure described above for IIb substituting the equivalent amount of benzyl chloride for bromobenzene. The product was obtained in 48–56% yield (based on the isatin consumed) as nearly colorless leaflets from 75 ml. of benzene, m.p. 170–173°, or as colorless needles from 50 ml. of 50% ethanol, m.p. 167–173°, the former solvent apparently giving the more nearly pure product (lit.[6a] m.p. 171–173°).

1-Amino-3-phenyldioxindole (VIb).—A mixture of 10.0 g. (0.044 mole) of 3-phenyldioxindole and 100 g. (0.088 mole) of 5% potassium hydroxide solution was heated to boiling under reflux for 3–4 hr. After the solution had been cooled, 3.1 g. (0.044 mole) of sodium nitrite was added and the resulting solution was added dropwise with stirring to 90 ml. of cold (0–5°), concentrated hydrochloric acid. During the diazotization, a small, variable amount of the reformed 3-phenyldioxindole separated. In a typical experiment the solid, which amounted to 1.8 g. (18%), was removed by filtering the cold diazonium solution onto a small amount of crushed ice. The formation of a diazonium solution was demonstrated by adding a few drops of the filtered solution to a basic solution of β-naphthol, whereby a bright red coupling product was formed.

The solution of diazotized α-phenylmandelic acid was added to a precooled (0–5°), vigorously stirred solution of 28.8 g. (3 × 0.044 mole, 1.5 equiv.) of stannous chloride dihydrate in 80 ml. of concentrated hydrochloric acid. A pale yellow solid, thought to be a tin salt, began to separate well before the addition of the diazonium solution was complete. The final mixture was stored overnight in the refrigerator, during which time the solid coagulated or reformed. The resultant solid was collected and washed thoroughly with water. After drying, the crude product weighed 8.1 g., m.p. 153–220°. Recrystallization from benzene gave 3.8 g. (44% based on the 3-phenyldioxindole consumed) of 1-amino-3-phenyldioxindole, m.p. 168.5–169.5°.

The compound was soluble in acetone, chloroform, ether, methanol, dilute sodium hydroxide (slowly) and hot benzene; slightly soluble in petroleum ether, carbon disulfide and chloroform and insoluble in water, 10% sodium bicarbonate and 2 *N* hydrochloric acid.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.12; H, 5.00; N, 12.01.

If the temperature of the final stannous chloride reduction mixture was kept below 5°, coagulation (and, hence, cyclization) of the product apparently did not occur. In such experiments considerable amounts of stannic ion could be detected in aqueous suspensions of the crude product and had to be removed by saturation of the solution with hydrogen sulfide.

1-Amino-3-benzyldioxindole (VIc).—The procedure used for the preparation of this compound was the same as that for the preparation of 1-amino-3-phenyldioxindole except that four equivalents of 10% potassium hydroxide were used in the hydrolysis. The amount of 3-benzyldioxindole recovered varied widely from one reaction to the next. In the most successful reaction 5.0 g. of 3-benzyldioxindole gave 1.0 g. (20%) of recovered starting material and 3.9 g. (92%, based on starting material consumed) of crude product. From one recrystallization from 50% ethanol 1.7 g. (40%) of 1-amino-3-benzyldioxindole was obtained as colorless needles, m.p. 158–160°. Further recrystallization from the same solvent raised the m.p. to 162.5–164°.

The compound was soluble in methanol, ethanol and chloroform; slightly soluble in benzene and carbon tetrachloride and insoluble in water and petroleum ether.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.85; H, 5.55; N, 10.88.

On repetition, the procedure did not yield consistent results and there was a considerable variation in the yield of pure material obtained. As in the case of 1-amino-3-phenyldioxindole, coagulation and cyclization appeared to proceed near 10°.

1-Benzalamino-3-phenyldioxindole.—A solution of 1.0 g. (0.0042 mole) of 1-amino-3-phenyldioxindole and 0.44 g. (0.0042 mole) of freshly distilled benzaldehyde in 25 ml. of ethanol was heated under reflux for 7 hr. The volume of the solution was reduced to *ca.* 10 ml. and 5 ml. of water was added. The product separated as cream colored needles, 1.25 g. (92%), m.p. 178–180°. Further purification by recrystallization from 95% ethanol raised the m.p. to 180–181.5°.

The compound was soluble (hot) in methanol, ethanol, chloroform, benzene and acetone and slightly soluble in water, and petroleum ether.

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.84; H, 5.06; N, 8.57.

4-Phenyl-3-cinnolinol (Vb).—A mixture of 1.00 g. (0.00417 mole) of 1-amino-3-phenyldioxindole, 8.42 ml. (0.00417 mole) of 1.984 *N* potassium hydroxide solution and 10 ml. of methanol was heated under reflux on the steam-bath for 2 hr. The hot solution was neutralized by the dropwise addition of 8.46 ml. (0.00417 mole) of 1.974 *N* hydrochloric acid, which effected the immediate separation of the canary-yellow product along with some of the starting material. After the mixture had been cooled, the solid was collected, washed thoroughly with water and recrystallized from 150 ml. of 95% ethanol, giving 0.42 g. (46%) of 4-phenyl-3-cinnolinol as yellow blades, m.p. 294–302° dec. An analytical sample was prepared by repeated recrystallization from ethanol, m.p. 300–302° dec. The pure material was moderately soluble in hot ethanol, hot methanol, hot benzene, chloroform and glacial acetic acid and was slightly soluble in cold benzene, petroleum ether, carbon tetrachloride, acetone and hot water.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 76.22; H, 4.61; N, 12.79.

The starting material could be recovered from the alcoholic filtrates and used again.

4-Benzyl-3-cinnolinol (Vc).—The procedure described for the preparation of 4-phenyl-3-cinnolinol was used with 1-amino-3-benzyldioxindole, but with much less success. The product was obtained in 10% yield as long, bright yellow needles, m.p. 222–225° dec. from benzene–Skellysolve B[15] (1:1). Alternatively a mixture of 1.5 g. (0.006 mole) of 1-amino-3-benzyldioxindole and 1.0 g. (0.025 mole) of sodium hydroxide in 25 ml. of 1:1 methanol–water was heated under reflux on the steam-bath for 2 hr. The warm solution was acidified to *p*H 6 by dropwise addition of acetic acid. The bright yellow product was recrystallized first from the minimum amount 95% ethanol and then from benzene–Skellysolve B[15] (1:1), giving 0.41 g. (29%) of 4-benzyl-3-cinnolinol, m.p. 222–225° dec. The compound was very soluble (hot) in methanol, ethanol, chloroform and acetone; slightly soluble in Skellysolve B[15] and petroleum ether and moderately soluble in benzene.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.21; N, 12.03.

6-Chloro-3-cinnolinol.[16]—The procedure of Alford and Schofield[5] was followed as closely as possible. From 5.0 g. of 5-chloro-2-nitromandelic acid 0.35 g. (lit.[5] 0.32 g.) of crude product was obtained, m.p. 230–251°. (Recrystallization of this material from ethanol gave 0.1 g. of very fine yellow needles, m.p. 246–248° dec. (lit.[5] 262–265°)). The infrared spectra of these materials in potassium bromide pellets indicated them to be a mixtures of 6-chloro-3-cinnolinol with some other unknown substance (with the latter probably predominating in the original product). After the aqueous filtrate (from which the original crude product had separated) had stood at room temperature for 7 days a second solid product had formed. This material was collected and air-dried to give 1.37 g. of yellow powder, m.p. 266–275°. After several recrystallizations from ethanol, 0.21 g. of very fine, yellow needles, m.p. 299–302° dec., was obtained. The infrared spectrum of this material was essentially the same as that of an authentic sample of 6-chloro-3-cinnolinol (m.p. 304–306° dec.).[17]

In two other experiments the yields of crude product (after reaction mixture had stood 7 days at room temperature) were 1.4 and 1.75 g. (m.p. variable between 245–275°). From these crude materials fairly pure 6-chloro-3-cinnolinol

(15) A petroleum solvent, b.p. 64–69°.

(16) We are indebted to Mr. William Bauer for the following experimental results.

(17) J. E. Dirks and W. F. Murdock, unpublished results.

could be obtained by dissolving the crude product in cold, 5% sodium hydroxide solution, treatment of the solution with charcoal followed by filtration, reacidification with acetic acid and recrystallization of the solid formed from a minimum of ethanol. Although the crude yields for the three runs were 44, 36 and 45%, the yields of pure material were quite variable, 8, 15 and 4%.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE, RENSSELAER, N. Y.]

Ethyl 3α-Phenyltropane-3β-carboxylate and Related Compounds

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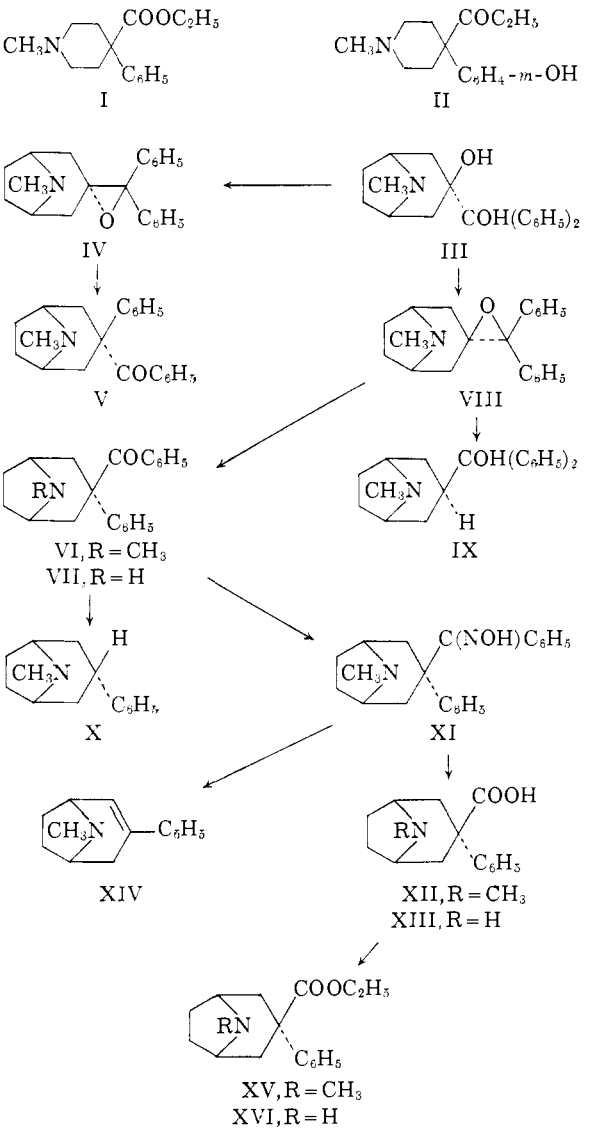
3α-Phenyl-3β-tropanyl phenyl ketoxime furnished 3α-phenyltropane-3β-carboxylic acid which on esterification gave the ethyl ester XV, the tropane analog of meperidine (I). The ketobemidone analog XXI was prepared from α-ecgonine amide by successive treatment with ethylmagnesium bromide and *m*-anisylmagnesium bromide, followed by treatment of the resulting diol with zinc chloride–acetic anhydride and then demethylation. Ethyl 3α-phenyltropane-3β-carboxylate (XV) was slightly more potent than meperidine as an analgesic.

Meperidine (I) and ketobemidone (II) are two members of the piperidine series of analgesics that have received some measure of clinical acceptance.[1] We thought it would be of interest to prepare the tropane analogs of these compounds and undertook the preparation of XV and XXI. If either of the new compounds showed interesting pharmacological properties we planned to replace the methyl group on the nitrogen of the tropane ring with a variety of larger radicals since it has been shown that such replacement of the N-methyl group of I resulted in a marked increase in potency.[2]

Previously we reported that 3α-diphenylhydroxymethyl-3β-tropanol (III) was converted to 3α-phenyl-3β-tropanyl phenyl ketone (VI) in the presence of zinc chloride and acetic anhydride.[3] We now find that brief exposure of III to this reagent results in the formation in good yield of the intermediate β-epoxide VIII. Assignment of this structure is based on the absence of hydroxyl and carbonyl absorption in the infrared spectrum and reductive cleavage with lithium aluminum hydride which furnished the known diphenyl-3β-tropanylcarbinol (IX).[3,4] Prolonged treatment of the epoxide with zinc chloride and acetic anhydride led to VI. The epoxide was assigned the β-configuration on the reasonable assumption that both the lithium aluminum hydride ring opening and the zinc chloride-catalyzed rearrangement occurred with inversion at C-3.

Boiling acetic anhydride converted III to the epimeric 3-benzhydrylidene tropane-α-epoxide (IV). The infrared spectrum of this product showed neither hydroxyl nor carbonyl absorption and the ultraviolet spectrum was virtually identical with that of the β-epoxide. The α-epoxide did not react with zinc chloride in acetic anhydride under the usual conditions at room temperature, but at 100° apparently 3β-phenyl-3α-tropanyl phenyl ketone (V) was formed. The infrared and ultraviolet



(1) O. J. Braenden and P. O. Wolff, *Bull. Wld. Hlth. Org.*, **10**, 1003 (1954); P. J. Braenden, N. B. Eddy and H. Halbach, *ibid.*, **13**, 937 (1955); N. B. Eddy, H. Halbach and O. J. Braenden, *ibid.*, **17**, 569 (1957).

(2) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); J. Weijlard, *et al.*, THIS JOURNAL, **78**, 2342 (1956); B. Elpern, L. N. Gardner and L. Grumbach, *ibid.*, **79**, 1951 (1957).

(3) M. R. Bell and S. Archer, *ibid.*, **82**, 151 (1960).

(4) (a) C. L. Zirkle, U. S. Patent 2,800,478 (July 23, 1957); (b) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg and M. J. Unser, THIS JOURNAL, **80**, 4677 (1958). 3-Benzoyltropane was first reported in ref. 4b and assigned the β-configuration by Bell and Archer (ref. 3). Since IX was prepared from this ketone (ref. 3) its configuration is as stated above.