[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Acid-Catalyzed Rearrangements of the γ-(Methylanilino)lactone of *cis*-β-(*p*-Bromobenzoyl)-β-methylacrylic Acid, and of *trans*-β-(*p*-Bromobenzoyl)acrylic Methylanilide, to Oxindoles[1]

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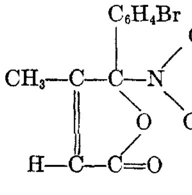
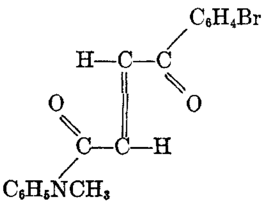
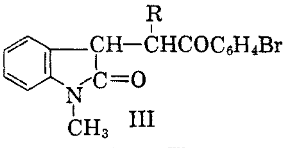
The structures of the acid-catalyzed rearrangement products of aroylacrylic "methylanilides" I and II to phenacyloxindoles III were shown by synthesis through condensations of *N*-methylisatin with appropriate aryl ketones followed by dehydrations and reductions. The properties and structures of the intermediate phenacylidineoxindoles are considered. A multistage rearrangement mechanism is proposed for formation of I, and a direct cyclization process for II.

In the study of acyclic and cyclic "amides" of β-(*p*-bromobenzoyl)-β-methylacrylic acid it had been observed that the action of hydrochloric acid–acetic acid mixture or methanolic hydrogen chloride on the cyclic "methylanilide" (the γ-methylanilinolactone, I), instead of hydrolyzing it, converted it into a new compound for which analysis appeared to support the empirical formula $C_{16}H_{16}BrNO$[4] but which also supports reasonably well that of an isomerization product $C_{18}H_{16}BrNO_2$.


I


II

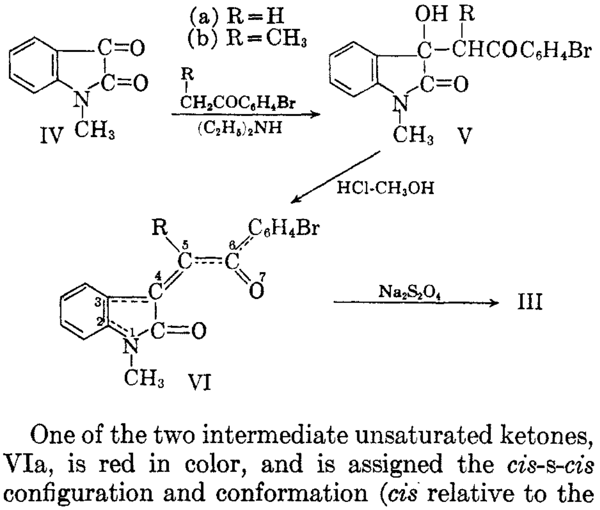
Similarly the *trans*-methylanilide of β-(*p*-bromobenzoyl)acrylic acid (II) was converted under acid conditions into an isomer, $C_{17}H_{18}NO_2$.[5] On the assumption that analogous isomerizations had actually occurred in both cases we have undertaken a study of these compounds and have established their structures as the *p*-bromophenacyloxindoles, III.


III

(a) R = H
(b) R = CH_3

Numerous attempts to hydrolyze or to reduce these compounds were without effect. Permanganate oxidation of one of them[5] to *p*-bromobenzoic acid had shown that the bromophenyl nucleus had not been involved. Ultraviolet and infrared absorption spectra were not immediately suggestive. Of the several types of structures that were empirically possible, only one, that of the oxindole III, fitted the facts and was consistent with the absorption characteristics of the compounds. The structures were then demonstrated by the following direct and unequivocal syntheses.

N-Methylisatin IV was condensed with *p*-bromoaceto- and propiophenones under mildly alkaline conditions, a procedure used successfully in other related cases.[6] The two resulting aldols V were then dehydrated by treatment with ethanolic hydrogen chloride to the unsaturated ketones VI. Reduction by sodium hydrosulfite converted these into the saturated phenacyl oxindoles III which showed no mixture melting point depressions with the rearrangement products of the two methylanilides, II and I, respectively.



One of the two intermediate unsaturated ketones, VIa, is red in color, and is assigned the *cis*-s-*cis* configuration and conformation (*cis* relative to the carbonyl groups) because examination of plane

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[1] This work was carried out under a research contract with the Office of Ordnance Research, U. S. Army.

[2] Present location, University of Georgia, Athens, Ga.

[3] (a) C. T. Clark, dissertation, University of Virginia, 1958. (b) Reported (with R. E. Lutz) at the ACS Meeting, September 1959, Atlantic City, N. J., abstr. p. 14p. Since the abstract was submitted we have decided against formula VII in favor of VI. (c) Paper (with R. E. Lutz), *J. Org. Chem.*, in press.

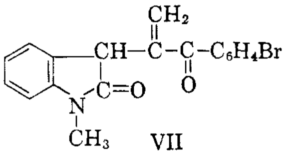
[4] R. E. Lutz and F. B. Hill, *J. Org. Chem.*, **6**, 175 (1941).

[5] R. E. Lutz and G. W. Scott, *J. Org. Chem.*, **13**, 284 (1948).

[6] (a) R. N. Dupois and H. G. Lindwell, *J. Am. Chem. Soc.*, **56**, 471, 2716 (1934). (b) H. G. Lindwell and J. S. Maclennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

scalar drawings[3a,7] shows only this form to be almost devoid of atom overlaps. The ultraviolet absorption maxima at 267.5 and 340 mμ, ϵ 21,000 and 13,400, are attributable to the principal chromophore numbered 1–7 in VI, to which the bromophenyl contributes.[8] The great facility of the reduction of this compound to IIIa is understandable in terms of the quinone-like unsaturated 1,4-dicarbonyl conjugation involved.

The other unsaturated ketone is more weakly colored, yellow. If it is the direct dehydration product of Vb, it presumably would exist in the least hindered form, VIb, of the four possible *cis*-, *trans*, and conformational forms, all of which involve extensive group overlaps according to plane scalar drawings.[3a,7] However, under the dehydrating conditions rearrangement to the α-methylene ketone form VII in which through-conjugation is broken, is possible but seemingly unlikely[cf. 3b] in view of two analogies.[3,9]



VII

The facility of sodium hydrosulfite reduction is in accord with the formulation VIb.

The ultraviolet absorption maximum at 261 mμ, ϵ 38,000 and the shoulder on the curve centering at 300 mμ, ϵ 8,000, seem to be more consistent with formulation VIb than with VII, as will be seen from the following considerations. The colorless saturated compounds IIIa and IIIb gave simple and almost identical ultraviolet absorption curves (λ_{max} 256, 255 mμ, ϵ 27,800, 26,900) which must represent the summation of absorptions of two fully independent chromophores, bromobenzoyl (ϵ *ca.* 15,300, assumed from that of β-(p-bromobenzoyl)-β-methylacrylic acid[8b]) and acylanilido (*ca.* ϵ 12,500, estimated by difference[cf. 10]), and this result provides a reasonable basis for expecting no significant absorption in the 300-mμ range and no color for a compound of the type VII where the two chromophores, in this case the acylanilido and vinyl bromophenyl ketone systems, are conjugatively independent. Actually the extremely high ϵ at 261 mμ with the very considerable shoulder on the absorption curve at 300 mμ, and the yellow color, are contrary to such expectations and are better explained in terms of the assigned structure VIb, assuming that there is sufficient steric interference with coplanarity of the β-methyleneoxindole and the bromobenzoyl chromophores to cause these systems to absorb largely independently of each other, but assuming also that there is insufficient interference entirely to suppress through-conjugation (numbered 1–7 in VIb).

The infrared absorption spectra of the compounds III and VI did not seem to furnish useful evidence regarding the possibility of an α-methylene group (VII); the absence of a methylene band at *ca.* 11 μ, like that observed for styrene and for penicillic acid,[11] does not exclude the possibility of this group because no such band appears in the spectra of two cases related to VIb which are known to have a carbonyl group conjugated with the methylene, namely methylene-1,2-dibenzoylethane[9a] and α-methylene-β-(p-bromobenzoyl)propionic acid.[3c] Differences in the carbonyl group absorptivities seemed significant, however. Each of the saturated ketones IIIa and IIIb showed a keto band at 5.95 μ and a lactam carbonyl band at 5.85 μ, which excluded hydroxyindole structures and served as reference points. The unsaturated ketone VIa with its very effective through-conjugation, showed appreciable lengthening of the wave length of the keto band to 5.97 μ and lowering of that of the lactam carbonyl to 5.78 μ, whereas the wave lengths of these two groups in VIb were practically the same as in IIIa and IIIb, and indicated that the through-conjugation, if it exists, has only a small degree of effectiveness.

The nuclear magnetic resonance spectrum at 60 megacycles subsequently obtained[12c] confirms the conclusion that the through-conjugated structure VIb is correct, by showing signals for two tertiary methyl groups at 2.48 and 3.12 p.p.m. from the internal reference, tetramethylsilane, the former representing the methyl group attached to the doubly bonded carbon.

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(7) (a) Plane scalar drawings analogous to those used in refs. c and d (below) were based on Pauling's bond distances and atomic radii. [(b) L. Pauling, *The Nature of the Chemical Bond*, Cornell University, Press, Ithaca, N. Y., 1944]. (c) L. P. Kuhn, R. E. Lutz, and C. R. Bauer, *J. Am. Chem. Soc.*, **72**, 5058 (1950). (d) R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Am. Chem. Soc.*, **73**, 4647 (1951).

(8) (a) *Cf.* H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, **74**, 4397 (1952). Absorptions of related chalcone systems: p-RC$_6$H$_4$CH═CHCOC$_6$H$_4$Br-p: R = OCH$_3$, λ_{max} 265, 348.5 mμ [(b) L. F. Ferguson and R. P. Barnes, *J. Am. Chem. Soc.*, **70**, 3907 (1948)]; R = N(CH$_3$)$_2$, λ_{max} 260, 420 mμ [(c) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, Jr., J. D. Smith, and J. W. Wilson, *J. Org. Chem.*, **14**, 988 (1949)].

(9) *Cf.* the relative instabilities of the methylene isomers of *cis* methyl-1,2-dibenzoylethylene and α-methyl-β-bromobenzoylacrylic acid [(a) P. S. Bailey, G. Nowlin, S. H. Pomerantz, J. V. Waggoner, and E. E. Kawas, *J. Am. Chem. Soc.*, **73**, 5560 (1951); (b) R. E. Lutz, P. S. Bailey, C.-K. Dien, and J. W. Rinker, *J. Am. Chem. Soc.*, **75**, 5042 (1953)].

(10) *N*-Acetyl-*N*-methyl-*o*-toluidine shows λ_{max} *ca.* 260–267 mμ [P. Grammaticakis, *Bull. soc. chim.*, 134 (1949)].

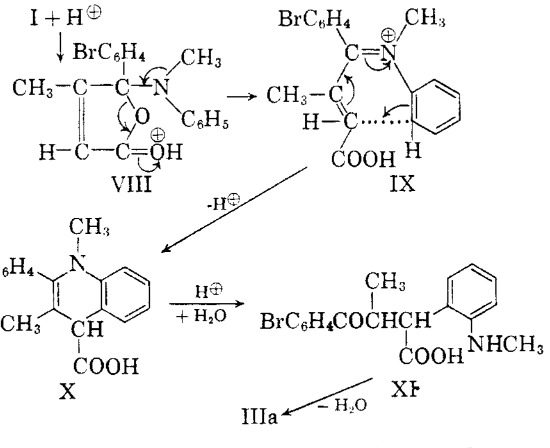
(11) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 87, 197.

(12) (a) Ultraviolet absorptions were determined at *ca.* $5 \times 10^{-5}M$ in 95% ethanol, using a Beckman DU spectrophotometer. Some of these determinations were by Joseph P. Feifer. (b) Infrared determinations were by Joseph P. Feifer on potassium bromide pellets, using a Perkin-Elmer Infracord spectrophotometer. (c) NMR data furnished and interpreted by LeRoy Johnson, Varian Associates.

Mechanistic Considerations. The mechanism of rearrangement of the methylanilinolactone (I) must involve several steps, because C—O and C—N bonds are broken and new C—N and C—C bonds are established. Passage through the acyclic *cis* or the *trans* methylanilide is precluded because the former rearranges under the reaction conditions to the latter which is stable[4]; and migration of the methylanilide nitrogen moiety from the α-carbon of I to the lactone carbonyl carbon also is precluded because had that happened the product isolated would have been the *trans* methylanilide.

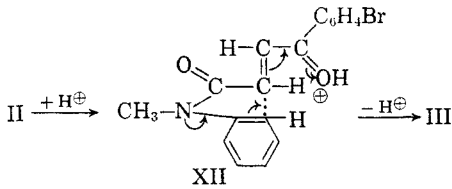
In this connection it is noteworthy that numerous unsuccessful attempts were made to displace aniline or methylaniline from the cyclic compounds of type I by other amines, aniline, methylaniline, and the stronger base dimethylamine, directly, or by nucleophilic attack at the lactam carbonyl. It should be noted also that unlike the methylanilinolactone I, the analogous parent γ-anilinolactone itself, instead of rearranging, undergoes hydrolysis with elimination of aniline. This difference is attributed[3c] to steric interference by the methyl group with hydrolysis, which affords more time and opportunity for the slow and competing rearrangement.

The mechanism VIII-XI is suggested in rationalization of the rearrangement of the methylanilinolactone I. In the first step protonation of the lactone carbonyl or bridge oxygen (VIII) leads through ring opening to an anil-onium ion IX, with cyclization to X, followed by ring contraction through hydrolytic enamine cleavage to XI, and ring reclosure through lactam formation to the oxindole IIIa.



The first step VIII → IX should go with ease, involving as it does disruption of a quaternary ketal type C—O bond, and the second, IX → X, is related to the Skraup ring closure or Claisen rearrangement. There is analogy for the reverse of the ring contraction X → IIIa wherein a compound of type III without the *N*-methyl group undergoes ring expansion to the type X under acid conditions.[6] However, in actual experiment under the conditions which rearranged 2-phenacyloxindole to 1,4-dihydrocinchophen,[6] the oxindoles III were recovered unchanged. It is postulated that ring contraction rather than retention of the 6-membered ring of X, and failure of ring expansion to occur (IIIa → X), is due to the great steric differences in group overlaps entailed in the presence of the *N*-methyl group which in the 6-ring would greatly lessen resonance stabilization, but which in the 5-ring would have relatively little effect. Plane scalar molecular drawings[7] of the two systems X and IIIa, with and without the *N*-methyl group, support this view.

For the mechanism of rearrangement of the simpler *trans* methylanilide II, which appears to be the species undergoing oxindole cyclization in this series (in marked contrast to the analogous β-methyl *trans* methylanilide which is not rearranged under the conditions[4]), it would appear that cyclization is direct, promoted by protonation of the α,β-unsaturated ketone system, as pictured in formulation XII. This reaction bears resemblance to the similar cyclizations of α-hydroxydiphenylacetic acid alkylanilides to *N*-alkyl-3,3-diphenyloxindoles.[13]



XII

EXPERIMENTAL[12]

3-(p-Bromophenacyl)-3-hydroxy-1-methyloxindole (Va). (For analogous preparations, see ref. 6b). A mixture of 350 ml. of absolute ethanol, 17.9 g. (0.118 mol.) of *N*-methylisatin,[14] 23.6 g. (0.118 mol.) of *p*-bromoacetophenone and 35 drops of diethylamine was heated to 50° and allowed to stand at room temperature overnight; yields of yellowish crystals 29.1 g. (70%), melting with decomposition at 167–171° before and after repeated recrystallizations from absolute ethanol. λ_{max}, μ, 2.90s, 3.39w, 5.88s, 6.14s, 6.24s, 6.33m, 6.64w, 6.77s, 6.99m.

Anal. Calcd. for $C_{17}H_{14}BrNO_3$: C, 56.68; H, 3.92. Found: C, 56.64; H, 4.02.

3-(p-Bromophenacylidine)-1-methyloxindole (VIa). (*Cf.* ref. 6b). A mixture of 25 ml. of absolute ethanol, 50 ml. of conc. hydrochloric acid, and 8 g. of Va was allowed to stand overnight at room temperature. The resulting precipitate (7.43 g.; 98%) was recrystallized from absolute ethanol; red, m.p. 194.8–196°. λ_{max} 267.5, 340 mμ, ε 21,800; 13,300; μ, 5.78s, 5.97s, 6.12m, 6.22s, (shoulders, 6.27s, 6.35w) 6.70w, 6.78m, 7.10m.

Anal. Calcd. for $C_{17}H_{12}BrNO_2$: C, 59.66; H, 3.53. Found: C, 59.57; H, 3.80.

Reduction to 3-(p-bromophenacyl)-1-methyloxindole (IIIa). (*Cf.* ref. 6b). Treatment of 4 g. of VIa in 50 ml. of 95% ethanol with 4 g. of sodium hydrosulfite dissolved in 20 ml. of water (heated on the steam bath for 2 hr.) gave 3.4 g. (85%) of IIIa. After recrystallization from ethanol, it melted at 156.5–157.5°. It was identified by mixture melting point with IIIa, the product[5] of the action of acetic–conc. hydrochloric acid mixture on II. λ_{max}, 256 mμ, ε 27,800; μ, 3.38w, 5.85s, 5.91s, 6.15m, 6.26s (shoulder), 6.32m, 6.66s, 6.77s, 7.03m.

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(13) R. F. Reeves and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 1086 (1942).

(14) W. Borsche and W. Jacobs, *Ber.*, **47**, 354 (1914).

3-(α-Methyl-p-bromophenacyl)-3-hydroxy-1-methyloxindole (Vb). A solution of 11.8 g. of *N*-methylisatin, 15.6 g. of *p*-bromopropiophenone,[3a,15] and 44 drops of diethylamine in 260 ml. of absolute ethanol, after standing at room temperature for several days, was partially evaporated and some water was added dropwise to precipitate 25.7 g. (97%) of Vb. After recrystallization from absolute ethanol it melted at 158–161°. λ_{max}, μ, 2.87s, 3.19w, 3.37w, 5.84s, 5.92s, 6.16s, 6.28m, 6.36m (shoulder), 6.66m, 6.78s, 6.86m, 7.00m.

Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 57.77; H, 4.31. Found: C, 57.69; H, 4.44.

3-(α-Methyl-p-bromophenacylidene)-1-methyloxindole (VIb). (*cf.* ref. 6b). A mixture of 7.25 g. of Vb in 21.5 ml. of absolute ethanol and 43 ml. of conc. hydrochloric acid, upon standing overnight at room temperature, gave 3.7 g. (54%) of VIb. After recrystallization from benzene it melted at 226–227°. λ_{max} 261 mμ, ε 38,000; shoulder, 300 mμ, ε 8,000; μ, 5.84s, 5.93s, 6.05m, 6.18s, 6.28s, 6.70m, 6.78s, 7.02m.

Anal. Calcd. for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96. Found: C, 60.44; H, 4.04.

3-(α-Methyl-p-bromophenacyl)-1-methyloxindole (IIIb). Reduction (as for VIa) of 0.22 g. of VIb in 70% ethanol by 0.22 g. of sodium hydrosulfite gave 0.2 g. of IIIb. After recrystallization from ethanol it melted at 137–139° and was identified by mixture melting point with the product[4] of the action of acetic–conc. hydrochloric acid mixture on I. λ_{max}, 255 mμ, ε 26,900; μ, 3.25w, 3.40w, 5.84s, 5.95s, 6.18s, 6.28s, 6.48w (shoulder), 6.68s, 6.79s, 6.89m, 7.05w.

Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5. Found: C, 60.1; H, 4.8.

Miscellaneous reactions. Only resinous product was obtained when the *trans*-methylanilide of (I) was subjected to the action of a 56:7 (by volume) mixture of acetic and conc. hydrochloric acids (refluxing for from 2 to 3 hr.); no VIb was isolated.

Numerous attempts to displace aniline or methylaniline or to force further reaction of the γ-anilino and methylanilinolactones (I) were unsuccessful; *e.g.*, heating the mixture at 150° for 2 hr., with or without added aniline or methylaniline hydrochloride (although in one case some VI was obtained), and heating a benzene solution saturated with dimethylamine and its hydrochloride.

Acknowledgment. We are indebted to Joseph P. Feifer for the determination of the infrared and two of the ultraviolet absorption spectra.

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(15) A. Collet, *Compt. rend.*, **125**, 717 (1897); **126**, 1577 (1898).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DE PAUL UNIVERSITY]

Formation of Tertiary Naphthylamines and Tetranaphthylhydrazines by *N*-Metallation[1]

EUGENE LIEBER[2] AND S. SOMASEKHARA

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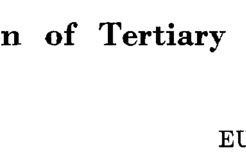
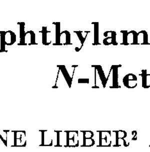
The discovery that the potassium metallation of 1,1′-dinaphthylamine (I) leads to significant yields of tetra(1-naphthyl)-hydrazine (II) has led to an extended study of the metallation of I and related secondary amines during which the syntheses of a number of tertiary amines have been achieved. Variation in the ratio of potassium to I and temperature did not increase the yields of II above 5%, the higher temperatures decreasing the yield. Diphenyl- and 2,2′-dinaphthylamines, respectively, failed to yield any evidence for hydrazine formation, under the conditions studied, while other related secondary amines gave only chromatogram fluorescent tests indicative of hydrazine formation. A free radical mechanism to account for I is proposed and discussed. The process is the reverse of the free radical dissociation of tetraarylhydrazines in solution.

In a preliminary communication Lieber[3] reported that a significant yield of tetra(1-naphthyl)-hydrazine (II) was obtained during an attempt to prepare the potassium salt of 1,1′-dinaphthylamine (I) by heating I under reflux with potassium in xylene.

I



II



III

In the same reaction, methylation experiments offered evidence that the potassium salt of I was not the intermediate involved in the formation of II. Further experiments with I using potassium in boiling xylene, with the exclusion of atmospheric oxygen, verified the formation of II, the yields being about the same (5%). Reagents such as potassium butoxide, potassium methoxide, and potassium amide, used under a variety of conditions, failed to produce any detectable amount of the potassium salt of I. In order to examine further the novel conversion of I to II, an extended study of the potassium metallation of I and related secondary amines was undertaken during the course of which the syntheses of a number of tertiary amines was achieved.

The metallation of I was carried out at various temperatures ranging from 110° to 200°. The experimental data revealed that the potassium salt of I was formed in good yields at lower temperatures.

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[1] This investigation was sponsored by the Basic Research Group, Corps of Engineers, U. S. Army, Fort Belvoir, Va. The authors gratefully acknowledge this assistance.

[2] Present address: Roosevelt University, Chicago 5, Ill., to whom all correspondence should be addressed.

[3] E. Lieber and S. Somasekhara, *Chem. and Ind.*, 1262 (1958).