# THE SYNTHESIS AND STEREOCHEMISTRY OF SOME ISATYLIDENEACETIC ACID DERIVATIVES\*.1

# R. L. AUTREY<sup>†</sup> and F. C. TAHK<sup>‡</sup> Department of Chemistry University of Rochester, Rochester, New York 14627

(Received in U.S.A. 8 June 1966, accepted for publication 12 July 1966)

Abstract—The preparations of *cis*- and *trans*-1-benzylisatylidene-3-acetaldehyde, *cis*- and *trans*-1-benzylisatylidene-3-acetic acid and some derivatives are described. Structures are assigned on the basis of NMR and  $pK_a$  measurements.

THE synthesis and structure determination of  $cis^2$  (1) and trans-1-benzylisatylideneacetaldehyde (2) and a number of their derivatives are reported.



These aldehydes and the related carboxylic esters, of known stereochemistry, should prove useful in the synthesis of alkaloids having an oxindole nucleus, such as



• Support of this work by the National Institutes of Health (Grant MH-08439) is gratefully acknowledged.

† To whom correspondence should be directed. Present address: Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, Mass. 02138.

\* National Science Foundation Fellow 1962-1965. Present address: Department of Chemistry, Kent State University, Kent, Ohio 44240.

<sup>1</sup> This work is presented in the Ph.D. thesis (1965) of F.C.T.

<sup>8</sup> The usage of *cis* and *trans* applied to these compounds and their derivatives in this article is that suggested for *cis/trans* double bond isomers by R. S. Cahn, C.K. Ingold and V. Prelog, *Experientia* 12, 81 (1956), footnote 13. It is essentially the result of considering these compounds as derivatives of maleic and fumaric acids. The thesis' employs the older convention of naming them as derivatives of *trans*- and *cis*-cinnamic acid, with consequent reversal of the nomenclature. The structural assignments are not reversed. mitraphylline<sup>3.4</sup> (3), rhyncophylline<sup>3</sup> (4, R = Et), cornynoxeine (4,  $R = -CH = CH_2$ ) and the more complex oxindole alkaloids gelsemine<sup>5</sup> (5) and gelsedine<sup>6</sup> (6).



A prominent structural feature of these substances is the 3,3-spiro disubstituted oxindole nucleus. The incorporation of the oxindole nucleus in previous syntheses of some of these structural types has been accomplished by oxidation of a precursor indole more or less closely related to the desired end product. The indole alkaloids of known structure were converted into their oxindole congeners by oxidation with butyl hypochlorite<sup>3.7</sup> or by lead tetraacetate.<sup>8</sup> A tryptamide derivative<sup>9</sup> was oxidized by N-bromosuccinimide<sup>10.11</sup> to an oxindole which was then converted in several steps to a derivative of rhyncophylline (4, R = Et). These several oxidative methods form the 3,3-spiro system by what is in essence a cationic rearrangement.

If, on the other hand, one starts from a preformed oxindole system such as is present in 1, then it seems more likely that subsequent attachment of additional groups will proceed by anionic reactions of the Michael<sup>12</sup> or Claisen condensations and related types.

The synthesis of oxindoles,<sup>18</sup> and more particularly, of oxindoles which are  $\alpha,\beta$ -unsaturated at C-3 (hereinafter, isatylidenes), has been the subject of many investigations, but even the most recent work appears to ignore the question of stereoisomerism about the trisubstituted double bond which many isatylidenes have.

- \* N. Finch and W. I. Taylor, J. Amer. Chem. Soc. 84, 3871 (1962).
- <sup>4</sup> For a brief general introduction to some of the oxindole alkaloids, see H.-G. Boit, *Ergebnisse* der Alkaloid-Chemie bis 1960 pp. 583-593. Akademie-Verlag, Berlin (1961). The field is an active one, and there is a large number of subsequent publications describing new alkaloids, structural assignments and syntheses, only a few of which can be cited here.
- \* F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Letters* No. 4, 1 (1959); \* H. Conroy and J. K. Chakrabarti, *Ibid.* No. 4, 6 (1959).
- \* E. Wenkert, J. C. Orr, S. Garratt, J. H. Hansen, B. Wickberg and C. L. Leicht, J. Org. Chem. 27, 4123 (1962).
- <sup>7</sup> Finch and Taylor<sup>a</sup> give a clear and concise summary of their own and other previous work (e.g. by B. Witkop and by W. O. Gotfredsen and S. Vangedal) on the oxidation of indole derivatives.
- \* N. Finch, C. W. Gemenden, I. H.-C. Hsu and W. I. Taylor, J. Amer. Chem. Soc. 85, 1520 (1963).
- \* E. E. van Tamelen, J. P. Yardley and M. Miyano, Tetrahedron Letters 1011 (1963).
- <sup>10</sup> W. B. Lawson and B. Witkop, J. Org. Chem. 26, 263 (1961).
- <sup>11</sup> R. L. Hinman and C. P. Bauman, J. Org. Chem. 29, 1206 (1964).
- <sup>18</sup> We appreciate the potential ambiguity in the Michael condensation with a cross-conjugated double bond of the kind present in 1. A manuscript describing some experiments to study the sense of this addition is in preparation.
- <sup>19</sup> W. E. Sumpter and F. M. Miller, *Heterocyclic Compounds with Indole and Carbazole Systems*. Interscience, New York, N.Y. (1954).

The lack of concern, apart from a single exception,<sup>14</sup> about this stereoisomerism may be understood on several bases: the early workers had no tool for elucidating this structural point, and the known compounds both early and recent appear for the most part to be homogeneous. We shall return to a discussion of this latter phenomenon in the sequel.

An attempt to prepare the aldehydes 1 and 2 directly, by condensation of 1benzylisatin (7) with acetaldehyde under a variety of conditions failed to give other products than acetaldehyde polymers, the reason for this being later discovered to be that the first intermediate (8) apparently prefers dealdolization to protonation and dehydration. Evidence for this preference comes from the attempted silver oxide oxidation of the aldol (9), which returned isatin.



More circuitous routes yielded the desired aldehydes and both related carboxylic acids. The relevant chemistry will be presented using the stereochemistry we ultimately assigned to the various isomeric pairs of substances, and then structural assignments, based principally on evidence from NMR spectroscopy, will be defended.

Proceeding upon a line previously explored briefly by Hallmann,<sup>15</sup> we prepared the Reformatsky ester 10 and attempted its dehydration to the  $\alpha,\beta$ -unsaturated ester 11 or its double bond isomer 12. Although the hydroxyl in ester 10 was both tertiary and benzylic, it was remarkably resistant to dehydration. The hydroxy ester was recovered unchanged after mild treatment with a small quantity of sulfuric acid in acetic acid, conditions used successfully<sup>16</sup> to dehydrate hydroxy esters 13, R = Et or CH<sub>2</sub>Ph, in which the hydroxyl was neither tertiary nor benzylic. More vigorous acid conditions led to resinification. We rationalize the stability toward acid catalyzed dehydration

<sup>14</sup> E. Wenkert, A. K. Bose and T. L. Reid, J. Amer. Chem. Soc. 75, 5514 (1953) convincingly assign structure i to the enol of 3-formyloxindole.



<sup>14</sup> G. Hallmann, Chem. Ber. 95, 1138 (1962).

<sup>10</sup> P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, J. Amer. Chem. Soc. 75, 5305 (1953).



in the following way.  $E_1$  elimination of water from the protonated alcohol places, in the transition state, partial positive charge adjacent to the carbonyl at C-2 and is hence not favorable.<sup>17</sup>

The Reformatsky ester was, however, susceptible to dehydration of its tosylate by  $E_2$  elimination. Thus, treatment of the hydroxy ester 10 with excess sodium hydride, followed by addition of toluenesulfonyl chloride at --78°, then by addition of methanol to generate methoxide, led to the unsaturated ester 11 as a single, orange compound of sharp m.p.

The same unsaturated ester was obtained in good yield by the addition of the



<sup>17</sup> A more elaborate, though no more revealing, defense of our observations may be made with Hückel MO theory. The difference in energy between the oxindole anion and cation is ca.  $0.6 \beta$ , an amount which is half that for the difference between cyclopentadiene anion and cation. This latter difference is a classic example of stability vs instability.

It isn't clear from his article that Hallmann<sup>14</sup> specifically sought to dehydrate il by acid, but the conditions under which it ultimately gave an unsaturated ester (isatylidene or isomeric quinolone?) were very vigorous.



anion of triethylphosphonoacetate to benzylisatin. TLC indicated the crude ester to be stereochemically homogeneous; by mixture m.p. and IR spectrum it was the same ester as that obtained by the dehydration of 10. It displayed the UV spectrum<sup>18</sup> characteristic of an isatylidene.

As our own work (vide infra) and that of others<sup>18b</sup> has shown, the addition of nucleophiles to isatylidene compounds is quite rapid by comparison with addition to many unsaturated carbonyl compounds. We were concerned that the isatylidene ester 11 might on attempted saponification revert to the original hydroxy ester 10. In the event, it did not, but we felt impelled to study the saponification of the hydroxy ester 10 despite unfavorable prognostications. Julian<sup>16</sup> reviews at some length, in describing his successful attempt to prepare oxindole-3-acetic acid, the unsuccessful previous attempts which involved alkaline conditions leading ultimately to quinolone derivatives (e.g. 14 or 15, R = H). Even more to the point is the observation<sup>19</sup> of the



rearrangement of ethyl 1-methyldioxindole-3-acetate (16) on hydrolysis to 1-methylquinolone-4-carboxylic acid (17). Saponification of the dioxindole ester 10 proceeded



smoothly and in good yield to the desired dioxindole acid 18 when the ester was treated in concentrated base briefly under such conditions that it had not all dissolved



before a new solid separated. We suspect that separation of the sodium salt as a solid may have been instrumental in preventing isomerization to the quinolone acid 14, R = benzyl. To make certain that isomerization had not occurred the acid was converted back to its ester with diazoethane.

The dioxindole acid proved as resistant to acid catalyzed dehydration as had its precursor ester, presumably for the same reason. Eventually, by the action of concentrated sulfuric acid on the acid 18 we obtained an unsatisfactory yield of the

<sup>&</sup>lt;sup>18</sup> • P. L. Julian and H. C. Printy, J. Amer. Chem. Soc. 75, 5301 (1953); \* R. L. Hinman and C. P. Bauman, J. Org. Chem. 29, 2431 (1964).

<sup>&</sup>lt;sup>19</sup> F. J. Myers and H. G. Lindwall, J. Amer. Chem. Soc. 60, 644 (1938).

isatylidene acid 19. It is possible that the low yield of product is caused by decar-



boxylation concomitant with dehydration. Such a reaction, characteristic of  $\beta$ -hydroxy acids, has been invoked<sup>20</sup> to explain the transformation of indole acetic acid, through the intermediacy of dioxindole acetic acid, to 3-methyleneoxindole by acidic solutions of hydrogen peroxide. The constitution of the acid apart from stereochemistry was indicated from its UV spectrum, which was clearly that of an isatylidene derivative.

Saponification of the isatylidene ester 11 was not attended by the readdition of hydroxide to the  $\alpha,\beta$ -unsaturated ester, but instead proceeded quickly to an isatylidene acid which was not identical to that prepared by the dehydration of the dioxindole-



acetic acid. The two acids were isomeric and could be thermally interconverted. The possibility of this interconversion was indicated by the m.p. of the *trans* acid 20. On being heated, it melted at  $160.5-163^\circ$ , resolidified and melted again at  $191.5-195.5^\circ$ . The m.p. of *cis* acid 19 from the dioxindole dehydration was  $191-195^\circ$ . Heating the



trans acid at  $145-160^{\circ}$  for 20 min gave a glassy mixture from which the *cis* acid could be obtained by direct crystallization. Owing to the ease with which the *trans* ester can be prepared by the Wittig reaction and its facile saponification, this thermal preparation of the *cis* acid was the easier of the two routes despite the unsatisfactory yield in the last step. The two acids were resolvable on TLC over Silica Gel G in methanol.

The thermal transformation of *cis* acid to *trans* was not demonstrated by isolation but was noted in the course of the NMR studies. A solution of the *cis* acid in dimethylsulfoxide at  $60^{\circ}$  showed changes in its NMR spectrum on standing for 90 min which indicated the presence of a 3:2 mixture of *trans: cis* isomers. Under the same circumstances the spectrum of the *trans* isomer was unchanged.

<sup>80</sup> R. L. Hinman and J. Lang, *Biochemistry* 4, 144 (1965).

906

The ease of saponification of the *trans* ester 11 deserves further comment. Using conditions as nearly the same as possible as those reported for the saponification<sup>21</sup> of ethyl benzoate and ethyl *m*-nitrobenzoate we determined a rough second order rate constant for the hydrolysis of ethyl *trans*-1-benzylisatylideneacetate (11). We found a rate constant about 23 times that of ethyl benzoate, and four tenths that of ethyl *m*-nitrobenzoate. This rate constant seems entirely reasonable in view of the electron-withdrawing power of the lactam carbonyl.

Two other transformations were performed to interrelate the members of this series of compounds. One of these two exemplified the exceptional electrophilicity of the isatylidene system, in that the addition of sodium borohydride to an ethanol solution of the isatylidene ester 11 effected immediate decolorization and we isolated the oxindole ester 21.



Recently, the borohydride reduction of a number of isatylidene derivatives was observed,<sup>32</sup> and more widely varied examples of carbon-carbon double bonds reduced by borohydride have been reported and other examples scattered through the literature collected.<sup>33</sup> Probably, the reduction of ethylideneoxindole to 3-ethyloxindole by hydroxylamine is similar.<sup>34</sup>

The other transformation was the preparation of the oxindole ester 21 by a different route. The *trans*-isatylidene acid 20 was reduced catalytically without cleavage of the benzyl group to 1-benzyloxindoleacetic acid 22, which gave the same ester 21 on treatment with diazoethane.



The facile borohydride reduction of the isatylidene ester 11 dissuaded us from pursuit of the *cis*- and *trans*-isatylidene-acetaldehydes (1 and 2) via the acids and we turned to a different route, again along a path pursued briefly by Hallmann.<sup>15</sup> He reduced benzylisatin to benzyldioxindole (23) which he alkylated with bromoacetal to obtain the acetal of benzyldioxindoleacetaldehyde 24.

This crystalline acetal yielded a gummy aldol 9 on gentle treatment with acid. Although the aldol was not well characterized, its constitution was unmistakable from the appearance of a band in the NMR spectrum at  $\delta = 9.79$  ppm. A crystalline

- <sup>39</sup> I. W. Elliott and P. Rivers, J. Org. Chem 29, 2438 (1964)..
- <sup>14</sup> S. B. Kadin, J. Org. Chem. 31, 620 (1966).
- <sup>44</sup> E. Wenkert, B. S. Bernstein and J. H. Udelhofen, J. Amer. Chem. Soc. 80, 4899 (1958).

<sup>&</sup>lt;sup>11</sup> E. Tommila and C. N. Hinshelwood, J. Chem. Soc. 1801 (1938).



dinitrophenylhydrazone was obtained from the aldehyde or directly from the acetal. Oxidation of the aldehyde by Jones's reagent gave the hydroxy acid 18, whereas the attempted oxidation by silver oxide led to dealdolization.



From the hydroxy aldehyde 9, or in better overall yield from the acetal 24, we obtained the isatylideneacetaldehydes 1 and 2 by the action of acid. A molar solution of the acetal in aqueous acetic acid was heated briefly with a small quantity of



sulfuric acid and diluted with water to give fine, garnet crystals of the two aldehydes in 60% yield. In the mixture so prepared, the ratio of *cis* isomer to *trans* was some three or four to one. A more dilute solution of the acetal, or of the aldehyde itself, in aqueous ethanol gave, on treatment with hydrochloric acid, a 21% yield of the unsaturated aldehydes in which the isomer ratio was indistinguishable from one to one. The two isomers had different  $R_f$ 's on Alumina G, and could be distinguished by their IR and NMR spectra.

The aldehydes had an unusually electrophilic carbonyl. The UV spectrum of the mixture in ethanol solution or in 2/1 methanol-chloroform solution was that of an ordinary isatylidene,<sup>18</sup> having a much diminished extinction beyond 300 m $\mu$  compared to the spectrum in cyclohexane. Similar proof of hemiacetal formation was evident from the NMR spectra in 2/1 methanol-chloroform solution, in which the signals for the aldehyde hydrogens had vanished and were replaced by a new doublet near 5-0 ppm. The aldehyde mixture was extraordinarily sensitive to light. A cyclohexane

solution, on standing 10 min at room temperature under nitrogen, changed from the characteristic garnet color to blue and began to deposit an ill-defined dark blue solid which we have not yet fully characterized.

# Evidence for the structural assignments

Significant features of the NMR spectra, which provide the principal foundation for the structural assignments, are summarized in Table 1. The most interesting aspects of these spectra are the observations and deductions to be made from the resonances of the aldehyde and vinyl hydrogens of the cis- and trans-1-benzylisatylideneacetaldehydes. Deshielded to a downfield position farther than the hydrogen of any other aldehyde that we have found reported are two clean doublets, centered at 11.13 and 10.53 ppm. These should be coupled only to the vinyl hydrogens of the two isomers, which cannot be located by simple inspection of the spectra. The aromatic region of the spectra contains the four (three in the case of special deshielding to be discussed) aromatic hydrogens of the oxindole nucleus spread from 6.69 to 7.41 ppm and the five aromatic hydrogens of the benzyl group as a singlet at 7.29 ppm. Consequently the appropriate vinyl hydrogens were located by spindecoupling experiments. Irradiation of the hydrogen at 10.53 with a decoupling frequency of 213 c/s caused the appearance of a sharp singlet at 7.01, and in a similar way the more deshielded aldehyde hydrogen was shown to be coupled to the less deshielded vinyl hydrogen at 6.70 ppm.

These correlations alone do not permit an unequivocal structural assignment, although they are indicative, in that the lactam carbonyl<sup>25</sup> may be expected to exert a stronger deshielding effect than the aromatic ring.<sup>26</sup> On this basis one expects the isomer with the more deshielded aldehyde hydrogen and the less deshielded vinyl hydrogen to have the aldehyde function *cis* to the lactam function. The observation which confirms this expectation is that of a strong downfield shift of the aromatic ring hydrogen<sup>27</sup> at C-4 in the isomer which has the less deshielded aldehyde hydrogen. In ten compounds, mostly 1-benzyloxindoles and 1-benzyldioxindoles, in which there is no reason to expect any unusual deshielding of any of the oxindole ring hydrogens, the C-4 hydrogen appears near 7.41 ppm. There appears shifted downfield to 8.00 ppm in the aldehyde mixture an unsharp doublet, having the same ratio of its integral to that of the benzyl methylene singlet at 4.88 as has the aldehyde doublet at 10.53. The mixtures examined varied in proportional concentration from 1:1 cis/trans to 5:1 cis/trans.

The only other isatylidene derivatives in which we have been able to examine a cis/trans pair are the carboxylic acids 19 and 20. Though we can make no argument from the relative position of the vinyl hydrogens, we can observe the shift of the ring hydrogen at C-4, it being 0.67 ppm farther downfield in one isomer than in the other Such a large shift seems explicable only on the basis of proximity to a carbonyl and we again assign the *trans* structure to the isomer with the more deshielded C-4 hydrogen. In the case of this pair an independent experiment confirms this structural assignment. The apparent  $pK_a$ 's of the two acids are: cis acid 19,  $pK_a =: 5.60$ ; trans acid 20,

<sup>&</sup>lt;sup>15</sup> P. T. Narasimhan and M. T. Rogers, J. Phys. Chem. 63, 1388 (1959).

<sup>&</sup>lt;sup>14</sup> C. E. Johnson, Jr, and F. A. Bovey, J. Chem. Phys. 29, 1012 (1958); J. S. Waugh and R. W. Fessenden, J. Amer. Chem. Soc. 79, 846 (1957).

<sup>&</sup>lt;sup>17</sup> P. A. Chopard, R. F. Hudson and R. J. G. Scarle, Tetrahedron Letters 2357 (1965).

	СНО	<i>H</i> –C-1'	HC-4•
	11-13	doublet $6.70$ J = $7.6$ c/s	7•46
	10-53	doublet 7·01 J = 6·3 c/s	8-00
/ СООН /! =0 СН2С6Н3			7.76
HOOC		6.83 sharp singlet	8·41
		6·98 sharp singlet	8.29
H <sub>2</sub> E <sub>6</sub> H <sub>5</sub>		7·24 ( ?)	8·52
MeCO N = 0		7.14	<b>8</b> ∙48

TABLE 1. NMR SPECTRA<sup>4,3</sup> OF ISATYLIDENE DERIVATIVES AND RELATED COMPOUNDS

Ten compounds (isatylidenes, oxindoles and dioxindoles) in which special deshielding is absent.

 $7.41 \pm 0.02$ 

Thirteen compounds (as above) in which there is a 1-benzyl group: position of the H—C-7, 6.69  $\pm$  0.02. Isatylideneacetone (26) H—C-7: 6.82. Seventeen compounds (including those dissolved in DMSO or trifluoroacetic acid) in which there is a 1-benzyl group: position of the five equivalent aromatic H: 7.29  $\pm$  0.02.

• Chemical shifts are reported in ppm on the  $\delta$  scale.

\* Compounds are dissolved in CDCl<sub>s</sub> unless otherwise noted.

<sup>c</sup> This *H* is visible in all cases in which it is specially deshielded, and in about half the cases in which it is not, as a doublet, J = -77 c/s, with further splitting, sometimes clearly discernible as J = -1.8 c/s. In the other half of the cases this *H* is concealed in varying degree by the adjacent 5*H* singlet of the benzyl group.

<sup>4</sup> Dissolved in DMSO.

• For no apparent reason we cannot find a singlet assignable to this H.

 $pK_a = 4.85$ . The *cis* acid has its strength lowered by chelation of the proton in a seven-membered ring.<sup>38</sup>

Using the structural assignments derived above, we are able to assign structures to other compounds in the series and in the literature (see the Table). The important question that arises is, why are all the trisubstituted isatylidene compounds that we have made (new or from the literature, e.g. 11, 25, and 26) only found as the *trans* isomer, except for the pair of acids and the pair of aldehydes? From measurements on models it seems clear that the answer to this question reflects an interplay of steric and electronic influences. However, the most obvious deduction from models is that there is no configuration or conformation of 27 which is free of compression and angle strain even if R = H. We therefore feel that it is pointless, in the absence of X-ray data, to present measurements which purport to show in detail the degree of strain in structures 27, in order to compare their relative stability. Let it suffice to say that the following generalizations appear plausible from crude measurements. For R = H, the stability order appears to be 27a > 27b, 27c > 27d, 27a > 27c. For R larger than H (but excluding OH for reasons of internal hydrogen bonding) the



order on steric grounds appears to be 27a < 27b, 27c < 27d, 27b > 27d; but on electrostatic grounds 27b < 27d. These orders may be reconciled in detail with the experimental observations. To give only two examples, we observe that the H at C-4 is less deshielded (0.59 ppm) by the *trans* aldehyde, presumably in conformation 27c, than in any of the other *trans* derivatives, presumably all in conformation 27d (e.g. the acetone derivative 25, shift: 1.11 ppm). And the acetone derivative 25 is forced very clearly for steric reasons to be 27b or 27d; and despite the fact that 27b seems less crowded than 27d, it is forced to the latter configuration by the strong dipole-dipole interaction of the two carbonyls in 27b. On the basis of these considerations we consider it likely that the monosubstituted isatylidenes (trisubstituted double bond) in the literature which have a carbonyl group  $\beta$  to C-3 will be found to be the *trans* isomers, and those which do not have a  $\beta$  carbonyl will be *cis* isomers.

In this connection we may note some results of Pietra and Tacconi<sup>29</sup> and ourselves which point again to the existence of strain in these isatylidene systems. The Italian

<sup>&</sup>lt;sup>28</sup> The especial stability of protons chelated in a seven-membered ring, rather than in a six-membered ring, is noted by Pimentel and McClellan. G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond* p. 175 Freeman, San Francisco (1960).

<sup>&</sup>lt;sup>30</sup> S. Pietra and G. Tacconi, Farmaco (Pavia) Ed. Sci. 16, 492 (1961).

authors, in dehydrating  $3-(2'-\infty + xy)$ -dioxindole (28) observed that the intermediate isatylidene 29 was unstable under the dehydration conditions and isomerized to  $3-(6'-\infty + xy)$ -oxindole (30). And although in our hands the preparation of cyclopentylideneoxindole (32) was straightforward, we were unable to



dehydrate 1-benzyl-3-(2'-oxocyclopentyl) dioxindole (33) to the isatylidene 34. Since, in the absence of the carbonyl group the compound forms easily enough, it seems



likely that the additional rigidity in a system with a ring which inhibits torsional distortion about the isatylidene double bond forces the carbonyl either too near the



C-4 hydrogen, or less likely, too near the lactam carbonyl, for the molecule to be stable. In the compound with the double bond not crossconjugated (e.g. 30), rotation about the C-3–C-1' bond relieves the steric and/or electronic repulsions.

# EXPERIMENTAL

# 1-Benzylisatin (7)

Finely powdered isatin (124 g) and NaH dispersed in mineral oil (Metal Hydrides; equivalent to 20.4 g of the base) were stirred vigorously under reflux in dry benzene for 11 hr. Benzyl bromide (171 g) was added over 30 min, and stirring and heating of the mixture were continued for 24 more hr. The hot solution was filtered from NaBr and cooled to yield 151 g benzylisatin in 3 crops. Recrystallization from EtOH-water yielded 135 g (68%) of long red needles, m.p. 133-5-135°, reported m.p. 131-132'.<sup>44</sup> If crystallization of benzylisatin occurred slowly or the long needles were left in the saturated mother liquors, small red prisms formed. They showed the same m.p. A similar apparent polymorphism is reported<sup>41</sup> for 1-methylisatin.

<sup>20</sup> H. Hellmann, G. Hallmann and F. Lingens, Chem. Ber. 86, 1346 (1953).

<sup>&</sup>lt;sup>31</sup> R. G. Ault, E. L. Hirst and R. A. Morton, J. Chem. Soc. 1653 (1935).

#### 1-Benzyldioxindole (23)

Benzylisatin (23.7 g) was added to a soln of NaBH<sub>4</sub> (4.72 g) in EtOH at 8°, with stirring. Within 4 min the temp had risen to 27°, the isatin had dissolved, and the color of the soln had faded completely. The soln was diluted with water (0.5 l) and cooled; the resulting oily suspension was scratched until crystallization occurred. The filtered, dried product was obtained as pale tan crystals (20.9 g, 87%) m.p. 136-137.5° (vac) of purity satisfactory for subsequent use. Recrystallization from benzene (77% recovery) afforded the benzyldioxindole as colorless platelets, m.p. 138.5-140° (vac), reported m.p. 138.5-139°.<sup>16</sup>

Failure to use low temp and an excess of borohydride resulted in the formation of highly colored intractable materials.

1-Benzyloxindole (31) was prepared from 1-benzylisatin.<sup>31</sup> The crude product, m.p. 50-63°, was not distilled but was recrystallized directly from EtOH-water to give fine needles, m.p. 65°0-65°5°. (Palazzo and Rosnati report m.p. 65°; Cornforth *et al.*<sup>34</sup> report m.p. 67°; Rinderknecht *et al.*<sup>34</sup> report m.p. 205-206°. This last report is probably erroneous, but the source of the error is not obvious. Their synthesis is not unambiguous, but the analytical data point to an isomer of 1-benzyloxindole. Staněk and Rybář<sup>34</sup> report the m.p. of 3-benzyloxindole to be 131°.)

### Ethyl 1-benzyldioxindole-3-acetate (10)

Ethyl bromoacetate (33·4 g), Zn turnings (13·1 g) and 1-benzylisatin (23·7 g) were mixed in 125 ml of dry benzene and heated on a steam bath for 5 hr with protection from moisture. The resulting mixture was poured with stirring into a slurry of 240 ml of 6N H<sub>3</sub>SO<sub>4</sub> and ice. The ppt was filtered and washed with cold benzene, cold 10% H<sub>3</sub>SO<sub>4</sub> and cold water. The crude, dried solid (18·6 g) was recrystallized twice from EtOH-water, then twice from benzene to yield 8·0 g (25%) of product, m.p. 137·8-138° (corr.), reported m.p. 138-139°.<sup>16</sup>

The UV spectrum (EtOH) is typical of 1,3-disubstituted dioxindoles: 257 (6,200) and 280 m $\mu$  (1,400).

### 1-Benzyldioxindole-3-acetic acid (18)

Method A. Ethyl benzyldioxindoleacetate (3.00 g) was saponified by brief heating at 70-80° in 33% (w/v) NaOHaq to which was added ca. 15% EtOH shortly before the end of the reaction. Soln was not complete before a new ppt formed. The mixture was cooled in ice, acidified with 10% HCl and extracted twice with ether. The crude dry residue (2.66 g) was recrystallized from EtOH-water to give 2.36 g (86%) of colorless rhombs, m.p. 177-179° (sintering). Further recrystallization did not readily improve the melting behavior; the best m.p. was 178.5-180° (vac). (Found: C, 68.92; H, 5.14; N, 4.86. Calc, for  $C_{17}H_{14}NO_4$ ; C, 68.68; H, 5.09; N, 4.71%.)

UV spectrum (EtOH): 257 (6,400) and 290 m $\mu$  (1,500). IR spectrum (KBr): 5-78 (COOH) and 5-90  $\mu$  (chelated lactam).

Esterification of the acid in THF with ethereal diazoethane returned the ester in 71% yield after recrystallization from benzene-cyclohexano-pet. ether, then aqueous EtOH. This ester showed m.p. 137-137.7° mixture with ester from the Reformatsky reaction, m.p. 137-137.8°.

Method B. Crude benzyldioxindoleactealdehyde (346 mg) in acctone soln was oxidized by dropwise addition of the Jones<sup>14</sup> reagent. The organic acid was obtained by dilution of the reaction mixture with water, extraction with ether, reextraction into 0.1N NaOH, acidification and extraction into ether. The dried ether yielded 218 mg of dark semisolid which was crystallized from EtOH-water to afford 148 mg (41%) of pale tan crystals. One recrystallization gave the acid as colorless crystals, m.p. 177--179°, mixture m.p. with sample from method A 178-179.5°. The IR spectra of the two samples in KBr were identical.

The acid could also be prepared from the aldehyde less satisfactorily by the action of KMnO<sub>4</sub> in dil phosphoric acid. Attempts to effect the conversion by the action of AgO led via a retroaldol reaction to the formation of benzylisatin, obtained in 23% yield after recrystallization to m.p.  $131\cdot5-134^\circ$ . The IR spectrum provided confirmation of identity.

<sup>88</sup> G. Palazzo and V. Rosnati, Gazz. Chim. Ital. 83, 211 (1953).

- <sup>44</sup> J. W. Cornforth, R. H. Cornforth, C. E. Dalgliesh and A. Neuberger, Biochem. J. 48, 591 (1951).
- <sup>44</sup> H. Rinderknecht, H. Koechlin and C. Niemann, J. Org. Chem. 18, 971 (1953).
- <sup>44</sup> J. Staněk and D. Rybář, Chem. Listy 40, 173 (1946),

<sup>44</sup> A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, J. Chem. Soc. 2548 (1953).

# Ethyl trans-1-benzylisatylidene-3-acetate (11)

Method A. NaH dispersion (equiv to 5.3 g of base) in mineral oil was washed free of hydrocarbon and covered with 300 ml dimethoxyethane dried from LAH. Triethyl phosphonoacetate (49.3 g) was added over a 15 min peroid; the mixture was stirred 5 more min; then benzylisatin (47.4 g) was added and the resulting soln stirred at  $50-55^{\circ}$  for 1 hr. The reddish soln was diluted with 600 ml water and extracted thrice with 500 ml ether. The ether extracts were dried, filtered and distilled *in* vacuo to leave an orange-red oil that crystallized on seeding. A TLC of the solid over Woelm alumina G in benzene showed only *trans* ester and a small amount of benzylisatin. Two recrystallizations from EtOH-water gave 46.1 g (75%) of orange crystals, m.p. 79.5-80.5°.

Method B. NaH dispersion (equiv to 0.33 g) was freed of mineral oil, then covered with 50 ml dry ether; to this was added 1.95 g of 10. After cessation of H evolution the suspension was cooled in Dry Ico-acetone and 1.146 g p-toluenesulfonyl chloride in 10 ml ether was added dropwise with stirring. After being stirred 2 hr at  $-78^{\circ}$ , the soln was allowed to warm to room temp. It was treated with 2 ml MeOH, then after 5 min it was poured into 50 ml water. A dried ether extract yielded oily material which was triturated with cyclohexane and seeded. Ultimately, after several recrystallizations there was obtained 0.475 g of starting material as colorless crystals, mixture m.p. 137:5-139°, and 0.483 g (35% based on unrecovered starting material) of yellow-orange needles, m.p. 79:5-80:5°, shown to be the desired product by mixture m.p., IR spectrum and TLC. In addition the mother liquors were shown by IR spectrum and TLC to consist largely of product ester and methyl p-toluenesulfonate.

An analytical sample of the ethyl trans-1-benzylisatylldene-3-acetate showed, after two recrystallizations from pet ether, m.p. 81-82°. (Found: C, 74.38; H, 5.83; N, 4.59. Calc. for  $C_{19}H_{17}NO_9$ : C, 74.25; H, 5.58; N, 4.56%).

UV spectrum (EtOH): 255 (23,500), 315 (6,700) and 415 m $\mu$  (1,000). IR spectrum (KBr): 5.87  $\mu$  (both carbonyls).

An attempt to dehydrate 10 or the related 18 by the method successfully used to dehydrate ethyl 3-oxindolylhydroxyacetate or ethyl 4-(3-oxindolyl)-3-hydroxypropionate to isatylidene deriv returned only starting materials as revealed by UV spectroscopy and recovery in good yield.

#### cis-1-Benzylisatylidene-3-acetic acid (19)

Method A. Benzyldioxindole-3-acetic acid (1-00 g) was dissolved in 5 ml conc  $H_8SO_6$  at 20°. After 8 min the soln was poured onto ice and extracted with ether, then chf. The dried extracts afforded a yellow gum which was crystallized from acetone to give 0-178 g, in two crops, of orange powder, m.p. 180-200°. On recrystallization from aqueous EtOH this afforded 87 mg (9%) of orange platelets, m.p. 191-195° (vac, sintering).

Method B. trans-1-Benzylisatylideneacetic acid (95.7 mg) was heated under N in a small tube in an oil bath at 145-160° for 20 min. Crystallization of the resulting glass from acetone yielded 16.1 mg (17%) of orange crystals, m.p. 193-196° (sintering) which were shown by IR and UV spectrum to be the *cis* isomer. (Found: C, 72.94; H, 4.74; N, 5.12. Calc. for  $C_{17}H_{18}NO_8$ : C, 73.11; H, 4.69; N, 5.01%.)

UV spectrum (EtOH): 257 (22,600), 262 (22,700), 308 m $\mu$  (5,600) and end absorption into the visible region. IR spectrum (KBr): 3.94 (COOH) and 5.85  $\mu$  (both carbonyls?). Apparent  $pK_a$  in 7:3::acetone:water<sup>47</sup>: 5.60.

#### trans-1-Benzylisatylidene-3-acetic acid (20)

Ethyl trans-benzylisatylideneacetate (1.54 g) was saponified at room temp in 25 min by the action of 0.5N NaOH in 1:1 EtOH-water. A dried ether extract of the acidified soln yielded 1.31 g orange foam which was crystallized from benzene to give 0.639 g (46%) orange crystals of the trans acid, m.p. 153-157° (sintering). One recrystallization from benzene and 3 from EtOH-water yielded the analytical sample as orange needles, m.p. 160.5-163° (vac), resolidifies as isomerization to *cis* isomer proceeds, m.p. 191.5-195.5°. (Found: C, 72.99; H, 4.79; N, 5.21. Calc. for C<sub>11</sub>H<sub>18</sub>NO<sub>8</sub>: C, 73.11; H, 4.69; N, 5.01%.)

UV spectrum (EtOH): 253 (23,300), 306 (6,100) and 390 m $\mu$  (800). IR spectrum (KBr): 3.81 and 3.92 (COOH of *cis* isomer formed by heat of pressing pellet, absent in soln spectra), 5.85  $\mu$ 

<sup>37</sup> M. J. S. Dewar and P. J. Grisdale, J. Amer. Chem. Soc. 84, 3546 (1962).

(broad, both carbonyls?); chf: 5.79 (shoulder) and 5.88  $\mu$ . Apparent pK<sub>a</sub> in 7:3 acetone-water: 4.85.

#### Ethyl 1-benzyloxindole-3-acetate (21)

Ethyl *trans*-benzylisatylideneacetate (3.25 g) in 40 ml EtOH was stirred with NaBH<sub>4</sub> (0.102 g). The original orange color of the soln was discharged instantaneously. Dilution with water, extraction with ether, and distillation of the solvent afforded 3.03 g viscous, pale greenish-yellow oil which by VPC (Dow Corning 11 Silicone Grease column at 225°, He flow rate 120 ml/min) gave the following 3 bands: unidentified material,  $R_1$  10 min, 0.5%; product ester,  $R_1$  15.5 min, 85%; starting material,  $R_1$  21.7 min, 14%. The yield of product, not corrected for recovered starting material, is thus 79%. An analytical sample was collected by VPC. (Found: C, 73.74; H, 6.32; N, 4.62. Calc. for  $C_{12}H_{12}NO_{2}$ : C, 73.77; H, 6.19; N, 4.53%.)

UV spectrum (EtOH): 251 (8,400) and 275 m $\mu$  (sh, 1,500). IR spectrum (CS<sub>2</sub>): 5.73 (saturated ester) and 5.79  $\mu$  (lactam).

#### 1-Benzyloxindole-3-acetic acid (22)

trans-Benzylisatylideneacetic acid (297 mg) was hydrogenated over 5% Pd/C in MeOH soln at atm press. Filtration of the catalyst, evaporation of the solvent and trituration of the residue with benzene gave crystals which, after 2 recrystallizations from benzene-cyclohexane, afforded 167 mg (59%) of benzyloxindoleacetic acid of analytical purity, m.p. 133-135°. (Found: C, 72.28; H, 5.39; N, 5.14. Calc. for  $C_{17}H_{18}NO_3$ : C, 72.58; H, 5.37; N, 4.98%.)

UV spectrum (EtOH): 252 (8,000) and 278 m $\mu$  (sh, 1,900). IR spectrum (chf): 2.8-4.3 (broad, COOH) and 5.84  $\mu$  (broad, shoulders, acid and lactam).

Esterification of the benzyloxindoleacetic acid with ethereal diazoethane gave, in 82% yield, the same ester as was obtained by reduction of ethyl *trans*-benzylisatylideneacetate. Identity was demonstrated by VPC, TLC and identical IR spectra as films and in chf soln.

# 1-Benzyldioxindole-3-acetaldehyde diethyl acetal (24)

This was prepared as described by Hallmann.<sup>14</sup> The use of crude benzyldioxindole lowered the yield of crude product to 55%. Two recrystallizations from benzene-petroleum ether gave colorless monoclinic crystals (76% recovery), m.p. 129:5-131° (corr), raised by further recrystallization from AcOEt-benzene to 131-132° (corr), reported m.p. 131-132°.<sup>14</sup>

#### 1-Benzyldioxindole-3-acetaldehyde (9)

The acetal 24 (2.00 g) in 20 ml acetone was stirred at room temp for 30 min with 20 ml 0.1M perchloric acid. The soln was diluted with water and extracted thrice with ether. The ether extract was washed with 5% NaHCO<sub>5</sub>aq then water, dried over MgSO<sub>4</sub>, filtered and distilled *in vacuo* to leave 1.53 g (97%) of crude aldehyde as a resin which showed the following appropriate spectral features: IR spectrum (chf): 2.97 (OH, broad), 3.50 and 3.65 (aldehyde CH), 5.78–5.88  $\mu$  (aldehyde and lactam, broad); NMR spectrum (CDCl<sub>6</sub>): aldehyde hydrogen at  $\delta = 9.79$  ppm.

1-Benzyldioxindole-3-acetaldehyde dinitrophenylhydrazone was prepared both from the crude aldehyde and directly from the acetal. The yield of crude dinitrophenylhydrazone from acetal, either directly or by isolation of the aldehyde and subsequent reaction was essentially quantitative. After two recrystallizations from AcOEt the derivative was obtained in 64% yield as yellow-orange crystals, m.p. 202:5-203:5° (vac, dec). (Found: C, 59:96; H, 4:34; N, 14:88. Calc. for  $C_{12}H_{10}N_5O_6$ : C, 59:87; H, 4:51; N, 15:18%.)

UV spectrum (EtOH): 355 mµ (23,100).

# cis- and trans-1-Benzylisatylidene-3-acetaldehyde (1 and 2).

Method A. Conc H<sub>2</sub>SO<sub>4</sub> (1 ml) was slowly added to a soln of 7·10 g of 24 in 20ml hot 3:1 (v/v) AcOHwater. The soln was heated on a steam bath for 10 min, diluted with 5 ml water, then allowed to cool slowly to 5°. The garnet-like crystals (3·02 g, 57%) which separated during the cooling were washed with cold solvent, then water, and dried. Their m.p. of 134·5-139° was raised by crystallization (89% recovery) from benzene-cyclohexane to 138-140·5°. The material so obtained is identical with that obtained by Method B, below, except that the mixture of isomers is estimated, by UV and NMR spectroscopy, to be cis:trans::3:1 or 4:1.

Method B. A soln of 1.77 g of 24 in 14 ml 2:1 EtOH-water was treated with 4.5 ml conc HCl

and the resulting soln was heated gently for 10 min. Ice (100 g) was added to the soln, whereupon a gum separated and was extracted into ether. The ether extract was washed with 5% NaHCO<sub>2</sub>aq, then water, dried over MgSO<sub>4</sub>, filtered and distilled *in vacuo* to leave 1.16 g (88%) of orange-brown semi-solid. This was crystallized twice from EtOH to afford 0.264 g (21%) garnet crystals. An analytical sample, m.p. 136.5–141°, was obtained by recrystallization from cyclohexane. From its spectral characteristics it appeared to be 1:1 mixture of *cis* and *trans* isomers. (Found: C, 77.50; H, 5.00; N, 5.43. Calc. for C<sub>17</sub>H<sub>18</sub>NO<sub>8</sub>: C, 77.55; H, 4.98; N, 5.32%.)

The pure material showed the following spectral characteristics: IR spectrum (chf): 3.51 and 3.64 (CHO), 5.84 (oxindole),  $5.97 \mu$  (CHO); UV spectrum (cyclohexane): 262 (25,500), 307 (7,800 sh), 317 (9,900), 330 (7,400), 347 (1,100 sh) and  $\sim 460 \text{ m} \mu$  (1,100).

The two IR absorptions at 3.51 and  $3.64 \mu$  appear to be associated specifically with the aldehyde C-H stretching vibration of the *trans* isomer. Mixtures in which the *cis* isomer predominates by 3 or 4 to 1 (NMR estimate) show much weaker absorption at these wavelengths.

Upon TLC over Woelm Alumina G in the solvent mixture 1-butanol-ether-benzene (2:10:88), the *cis/trans* mixture showed two well-resolved spots of  $R_r$  0.63 and 0.71. However, UV spectra of the materials recovered from the spots indicated that decomposition was occurring to an appreciable extent.

### trans-Isatylidene-3-acetone (26)

This was prepared as reported.<sup>24</sup> The compound, obtained in 9.5% overall yield after 2 recrystallizations of the aldol from acetone, then 2 recrystallizations of the unsaturated ketone from EtOH and one from benzene, was in the form of fine, matted, orange neddles, m.p. 166.5–169.5° (vac), Braude and Lindwall report m.p. 168–171°; Pietra and Tacconi<sup>34</sup> report m.p. 174°.

UV spectrum (EtOH): 255 (19,000), 322 (7,100), and 425 m $\mu$  (1,400). IR spectrum (chf): 2.91 (NH), 5.81 (lactam) and 5.92  $\mu$  (unsaturated ketone).

#### 1-Benzyldioxindole-3-acetone

Benzylisatin (21.5 g) in acetone (69.5 g) and diethylamine (7.0 g) was kept at 45° for 5 hr. The soln was then concentrated to a volume of 35 ml and chilled. The crystals that separated in 2 crops were combined and recrystallized from benzene to give 10.1 g (65%) crystals, m.p. 160–161°. The analytical sample was obtained as colorless, mica-like platelets, m.p. 160–161°, after 3 recrystallizations from EtOH-water. (Found: C, 73.13; H, 5.85; N, 4.80. Calc. for  $C_{12}H_{17}NO_3$ : C, 73.20; H, 5.80; N, 4.74%.)

UV spectrum (EtOH): 258 (6,800) and 287 m $\mu$  (1,500). IR spectrum (chf): 2.94 (broad, OH), 5.80 (lactam) and 5.85  $\mu$  (sh, ketone).

#### trans-1-Benzylisatylidene-3-acetone (25)

Benzyldioxindole-3-acetone (1.00 g) was dissolved in a soln of 1.15 ml conc HCl in 4.5 ml EtOH. This soln was heated 7 min on the steam bath to give a deep red soln that was poured into ice and water. An ether extract was obtained, washed with 5% NaHCO<sub>2</sub>aq and water, and dried over MgSO<sub>4</sub>. Removal of the ether left a red glass which crystallized on trituration with acetone. A recrystallization of these crystals from acetone, then another from EtOH-water gave 246 mg (26%) of orange platelets, m.p. 107.5-109°. (Found: C, 78.24; H, 5.69; N, 5.16. Calc. for C<sub>10</sub>H<sub>15</sub>NO<sub>3</sub>: C, 77.96; H, 5.45; N, 5.05%.)

UV spectrum (EtOH): 259 (20,000), 324 (6,900) and 427 m $\mu$  (900). IR spectrum (KBr): 5.82 (lactam) and 5.93  $\mu$  (unsaturated ketone).

#### 1-Benzylcyclopentylideneoxindole (32)

Benzyloxindole (1-12 g), cyclopentanone (0.84 g), pyrrolidine (0.20 ml) and Na<sub>2</sub>SO<sub>4</sub> (2.0 g) were mixed in 10 ml benzene and heated under reflux for a week. The filtered soln was washed with 3% HCl and water, and dried. Removal of the solvent *in vacuo* left a solid mass which was recrystallized from cyclohexane to yield 908 mg (63%) needles, m.p. 132-134°. A second recrystallization gave

<sup>14</sup> F. Braude and H. G. Lindwall, J. Amer. Chem. Soc. 55, 325 (1933).

<sup>\*</sup> S. Pietra and G. Tacconi, Farmaco (Pavia) Ed. Sci. 13, 893 (1958).

UV spectrum (EtOH): 256 (sh, 28,700), 263 (34,500), 285 (sh, 6,500), 294 (8,000), 304 (sh, 6,400) and 350 m $\mu$  (1,500). IR spectrum (CS<sub>1</sub>): 5.85  $\mu$  (lactam)

# 1-Benzyl-3(2'-oxocyclopentyl) dioxindole (33)

Benzylisatin (11.9 g), cyclopentanone (16.8 g) and pyrrolidine (1-0 ml) were stirred at 35-40°. A flocculent ppt formed, and after 1.5 hr, the addition of 10 ml benzene was required to maintain stirring. After 4.5 more hr, the reaction mixture was diluted with 100 ml ether and filtered, to give 11.5 g (72%) pale greenish crystals, m.p. 174-177° (dec). Recrystallization from benzene, then EtOH, gave the analytical sample as colorless platelets, m.p. 176-180° (vac, dec). (Found: C, 74.77; H, 6.24; N, 4.47. Calc. for C<sub>20</sub>H<sub>18</sub>NO<sub>8</sub>: C, 74.75; H, 5.96; N, 4.36%.)

IR spectrum (KBr): 3.01 (OH), 5.76 (5-membered ketone) and 5.90  $\mu$  (lactam).

Acknowledgement—We are pleased to acknowledge the assistance of Dr. L. D. Colebrook, who performed the decoupling experiments in NMR spectroscopy, obtained many of the other NMR spectra, and made some calculations along the lines suggested by references 25 and 26 which may be interpreted as further support for the structural assignments of the *cis* and *trans* aldehydes.