[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. VI. The Structure of Neber's Lactam. A New Synthesis of 3-Cinnolinol[1,2]

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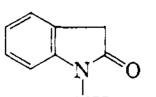
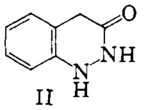
Neber's lactam, the lactam formed either by the reduction of 3-cinnolinol with zinc and sulfuric acid or by thermal cyclization of *o*-hydrazinophenylacetic acid, has been shown to be 1-aminoöxindole. Oxidation of the lactam with lead tetraacetate gave 3-cinnolinol.

The preparations of 1-aminoöxindole[5,6] (I) and of 1,4-dihydro-3(2H)-cinnolinone[7] (II) have been reported by Neber and co-workers. The latter was said to have been prepared by Neber's student, Bössel,[8] by the reduction of 3-cinnolinol (3-hydroxycinnoline, 3(2H)-cinnolinone) (III) with zinc and sulfuric acid, and the former was prepared by the thermal cyclization of *o*-hydrazinophenylacetic acid (IV). Although the assigned structure of the reduction product of III has not been supported by any published evidence, it apparently has been accepted by most workers in the field. Thus, Alford and Schofield[9] have assigned the structure 1,4-dihydro-2-methyl-3-cinnolinone to the reduction product of 2-methyl-3-cinnolinone, presumably by analogy with the reported results of Bössel. The structure of the cyclization product of IV appears to have been fairly well established by Neber,[5,6] the principal, but not only, evidence being the formation of oxindole on treatment of the product with nitrous acid. Our interest in these reactions arose from the observation that, according to the infrared spectra, the products obtained by the two different routes described above were identical. This communication describes our reinvestigation of the structure of this substance, which we have labeled Neber's lactam and which we believe to have the structure I.


I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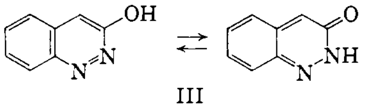
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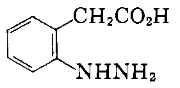
IV

The preparation of the lactam was carried out essentially as described by Neber,[5,7] although several procedural improvements were made, which are described in the experimental section. The overall yields by the two routes from the respective starting materials, *o*-nitrophenylacetic acid and III, were 50 and 50–76%.

Neber's[5] observation that the reaction of the lactam with nitrous acid gave oxindole (V) was confirmed but the yield of oxindole was low (23%). Furthermore, the validity of this chemical evidence for the structure I was somewhat in doubt, for it was possible to write fairly reasonable mechanisms for the formation of V from either I or II. Further doubt as to the validity of any chemical evidence was evoked by the discovery that the lactam could be oxidized by lead tetraacetate to III in 78% yield. The oxidation could be carried out in much lower yield with mercuric acetate but not with hydrogen peroxide in acidic or alkaline media, Fentons' reagent, potassium permanganate, dilute or concentrated nitric acid or iodine and potassium carbonate. Although this result, together with the formation of the lactam by the mild reduction of III, might at first sight appear to be fairly good evidence for the structure II, again fairly reasonable mechanisms could be written for the formation of III from either I or II (*vide infra*). Indeed, one might argue that the lactam was in fairly mobile equilibrium between I and II and that chemical reactions would give evidence only of that species most capable of reacting. Such an argument might explain the other observed reactions of the lactam: (1) the ready formation of a hydrochloride, (2) the reaction of the lactam with benzaldehyde to form 1-benzalaminoöxindole,[10,11] (3) the reaction with benzaldehyde in the presence of acetic anhydride to yield 1-acetylamino-3-benzaloxindole,[12] and (4) the formation of a monobenzoyl derivative.[13]

In the final analysis structural information from infrared and nuclear magnetic resonance (n.m.r.) spectra was used to assign a most reasonable structure to the lactam. For this purpose the

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[1] Paper V, THIS JOURNAL, **80**, 6609 (1958).

[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 of P. L. Creger (June, 1957) and the M.S. Thesis of R. L. Zey (January, 1959).

[3] Eastman Kodak Co. Fellow, 1955–1956.

[4] Standard Oil Co. (Indiana) Fellow, 1958–1959.

[5] P. W. Neber, *Ber.*, **55**, 826 (1922).

[6] P. W. Neber and H. Keppler, *ibid.*, **57**, 778 (1924).

[7] P. W. Neber, G. Knoller, K. Herbst and A. Trissler, *Ann.*, **471**, 113 (1929).

[8] G. Bössel, Inaug. Diss. Tubingen, 1925; *Chem. Zentr.*, **100**, **II**, 3015 (1929).

[9] E. J. Alford and K. Schofield, *J. Chem. Soc.*, 1811 (1953).

[10] A somewhat related example is the reaction of 1,4-phthalazinedione with benzaldehyde to yield N-benzalaminophthalimide (H. D. K. Drew and H. H. Blatt, *J. Chem. Soc.*, 16 (1937)).

[11] The product of the reaction between benzaldehyde and the lactam was reported by Neber and Keppler[6] to be 1-amino-3-benzaloxindole, but the infrared spectrum of the product obtained in the present work indicated no free –NH$_2$ group and other properties supported the N-benzalamino structure (see Experimental section). Neber and Keppler reported that *o*-, *m*- and *p*-nitrobenzaldehyde gave the corresponding 1-(*o*-, *m*- and *p*-nitrobenzal)-aminoöxindoles when *o*-hydrazinophenylacetic acid was substituted for the lactam.

[12] Structural assignment was based on the infrared spectrum (Table I) which indicated the presence of an N–H group as well as two carbonyl groups.

[13] Although Neber and Keppler[6] reported the preparation of both a mono- and a dibenzoylated derivative, in the present investigation only the monobenzoylated product could be obtained.

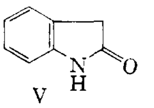
TABLE I

INFRARED SPECTRA[a]

Compound	ν(C=O) region[b]	ν(N—H) region[c]
Acetanilide	1686s	3489s, 3390w
N-Methylacetanilide	1646s	
α-Acetylphenylhydrazide	1646s, 1615w[d]	3325m, 3290sh, 3325bbw
N-Benzalaminoacetanilide	1679s	
β-Acetylphenylhydrazine	1685s	3430m, 3368sh, 3345m
β-Acetyl-α-methylphenylhydrazine	1687s, 1667m	3414w, 3350m, 3321m
N-Acetyl-*unsym*-dimethylhydrazine	1687s, 1665w	3430w, 3334w, 3301w
Oxindole	1722m, 1702s	3443s
N-Methyloxindole	1698s	(3394w)
Neber's lactam (N-aminoöxindole)	1698s, 1657w[d,e]	3384sh, 3347m, 3291w, 3120bbw
1-Benzalaminoöxindole	1708	
3,4-Dihydro-2(1H)-quinolone	1688sh, 1676s	3407s
1-Amino-3,4-dihydro-2(1H)-quinolone	1669s	3331m, 3270sh, 3212w
1-Benzalamino-3,4-dihydro-2(1H)-quinolone	1679s	
2(1H)-Pyridone	1679sh, 1658s[f]	3250w, 3100m[f]
1-Methyl-2(1H)-pyridone	1668s[g]	
1-Amino-2(1H)-pyridone	1668[g]	3330m, 3192m[g]

[a] Run using Perkin–Elmer model 21 double beam spectrometer with chloroform solution, the chloroform being dried just prior to use by passage through a 20 × 3.5 cm. column packed with a 1:1 mixture of chromatographic grade silicic acid and Celite 545 which had been dried overnight at 140–150°. This procedure was demonstrated to be as effective for the removal of alcohol as the conventional washing with sulfuric acid and with water followed by drying over calcium chloride and distilling. [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] Run with LiF prism; concentration was 0.005 M in 5-mm. cell for $-\underset{|}{N}-H$ compounds and 0.025 M in 5-mm. cell for $-\overset{|}{N}-NH_2$ compounds. Relative intensity designations refer only to peaks in the ν(N–H) region. [d] NH_2 deformation. [e] Deuteration by refluxing 0.3 g. of the lactam with 3 ml. of deuterium oxide (in which almost all of the lactam dissolved), precipitation by cooling and repetition of this procedure with fresh deuterium oxide four times gave a product in the spectrum of which this peak was no longer present. [f] Reported for a carbon tetrachloride solution by J. A. Gibson, W. Kynaston and A. S. Lindsey (*J. Chem. Soc.*, 4340 (1955)). [g] Reported for a carbon tetrachloride solution by K. Hoegerle and H. Erlenmeyer (*Helv. Chim. Acta*, **39**, 1203 (1956)).

approximate models α-(VI) and β-acetylphenylhydrazine (VII) were employed in conjunction with a number of other related substances. The infrared data, all for chloroform solutions,[14] are summarized in Table I. Two regions of the infrared spectrum, the ν(N—H) and ν(C=O) regions, were the most useful and discussion will be limited to these.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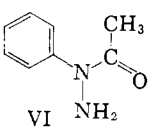
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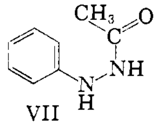
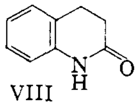

VII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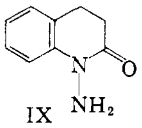
IX

Interpretation of the ν(C=O) region was by far the simpler for it was immediately apparent that the high value for the ν(C=O) frequency for the lactam (1698 cm.$^{-1}$) was more nearly that expected for a five-ring than for a six-ring lactam. For example, the ν(C=O) band for 3,4-dihydro-2(1H)-quinolone (VIII) appears as a sharp peak at 1676 cm.$^{-1}$ with a shoulder at 1688 cm.$^{-1}$, whereas that for V appears as a sharp peak at 1722 cm.$^{-1}$ with a shoulder at 1702 cm.$^{-1}$. That the frequency for the lactam was somewhat lower than that for V was to be expected, for the ν(C=O) frequencies for VI and VII were 1646 and 1685 cm.$^{-1}$, respectively, compared with 1686 cm.$^{-1}$ for acetanilide. Thus, there appears to be a frequency lowering effect on the carbonyl band of an amide when an NH_2 group is substituted on the amide nitrogen. Actually, the ν(C=O) frequency for the lactam was identical with that for N-methyloxindole. This exact correspondence probably was fortuitous for, although the carbonyl frequencies of three of the N-amino amides (α-acylhydrazines) in Table I are approximately equal to those of the corresponding N-methyl amides and are much lower than those of the unsubstituted amides, in an example to be described in a later communication the ν(C=O) frequency is about equidistant between those of the N—H and the N—CH_3 compounds.

It seems probable that the frequency lowering effects of the N-methyl and N-amino groups have different origins. The lowering caused by the N-methyl group may be due to the inductive effect of that group, which would be expected to stabilize the polar form of the amide and thereby cause a decrease in the double bond character of the carbon–oxygen bond. The lowering caused by the N-amino group (which by induction should be electron-withdrawing and, hence, should destabilize the polar form of the amide group) is probably a result of intramolecular hydrogen bonding between the N-amino and the carbonyl groups. The latter interaction probably is responsible also for the characteristic contour (which differs markedly from that usually associated with the —NH_2

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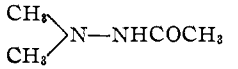
[14] Although most of the spectra were run also in carbon tetrachloride and in dioxane as well as in mulls and KBr wafers, the chloroform solution spectra were by far the most useful.

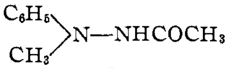
group) of the bands in the ν(N—H) region of these compounds. When this hydrogen bonding is destroyed (as in the reaction of the N-amino compounds with benzaldehyde), the value of the ν-(C=O) frequency is raised to near that for the unsubstituted amide.

Because of the increased number of variables contributing to the determination of the positions of the bands appearing in the ν(N–H) region, this region of the spectrum was more difficult to interpret. Thus, VI showed a relatively sharp, medium peak at 3325 cm.$^{-1}$, a shoulder at 3290 cm.$^{-1}$ and a very broad, low peak at 3225 cm.$^{-1}$, and IX showed a relatively sharp, medium peak at 3331 cm.$^{-1}$, a diffuse shoulder at 3270 cm.$^{-1}$ and a fairly sharp, weak peak at 3212 cm.$^{-1}$. The location of these peaks is not unreasonable in view of the ν(N–H) frequencies reported[15] for N,N-dimethylhydrazine in the liquid state, 3298 and 3126 cm.$^{-1}$; however, any exact assignment of the various observed frequencies would have to take into consideration factors such as the configuration around the C–N bond of the amide (definitely *cis* in XI but at present unknown for VI), possible appearance of the overtone of the ν(C=O) frequency (as well as Fermi resonance involving the overtone) and intramolecular hydrogen bonding.

By way of contrast, VII showed strong, sharp bands at 3431 and 3345 cm.$^{-1}$ with a definite shoulder at 3368 cm.$^{-1}$. Although three bands can be accommodated by accepting various rotational configurations around the amide C–N bond coupled with hydrogen bonding effects, it is not as easy to rationalize the three well-defined peaks observed for N-acetyl-*unsym*-dimethylhydrazine (X) and β-acetyl-α-methylphenylhydrazine (XI) at 3430, 3334 and 3301 cm.$^{-1}$ and 3414, 3350 and 3321 cm.$^{-1}$, respectively. Possibly these are due to combinations of rotational isomerism coupled with the appearance of the amide carbonyl overtone (calculated roughly to appear at about 3330–3374 and 3334–3374 cm.$^{-1}$, respectively) or to rotational isomerism and Fermi resonance between the ν(N–H) and the ν(C=O) overtone vibrations.


$(CH_3)_2N—NHCOCH_3$

X


$(C_6H_5)(CH_3)N—NHCOCH_3$

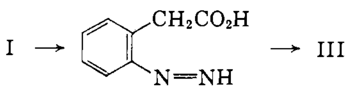
XI

In any event the spectrum of Neber's lactam in the ν(N–H) region resembled fairly closely those of VI and IX and showed a relatively sharp, medium band at 3347 cm.$^{-1}$, a weak but sharp band at 3291 cm.$^{-1}$, a very broad, weak band at about 3210 cm.$^{-1}$ and a low shoulder at 3384 cm.$^{-1}$. The general over-all contours of the bands in this region were quite similar for VI, IX and the lactam.

In the n.m.r. spectrum[16] of VI the NH signal appeared as a rather broad peak at 5.22 τ, the methyl peak at 7.97 τ and the five aromatic protons at 2.48–2.83 τ (centered at 2.65 τ). The methyl peak was much broader than expected and was actually found to be temperature dependent. When the solution of VI was cooled, an additional methyl peak appeared a few p.p.m. down-field (lower τ). Very probably these observations may be explained as being due to hindered rotation around the C–N bond of the amide unit. The n.m.r. spectrum of VII also showed two methyl peaks, the larger at 7.98 τ and the smaller at about 7.90 τ, and these were broadened by increasing the temperature of the sample. In the spectrum of VII there were two signals from the amide N–H at about 4.05 and 3.72 τ as well as a rather broad peak due to the α-N–H group at 2.32 τ. In this instance the signals from the protons on the benzene ring were spread out from about 2.55–3.38 τ, possibly indicating some double bond character between the nitrogen and the ring as well as between the amide carbon and nitrogen. The study of the hindered rotation of molecules of this general type is being continued.

The n.m.r. spectrum of Neber's lactam showed the CH_2 group signal at 6.55 τ, the aromatic protons at 2.53–3.18 τ, (centered at 2.90 τ) and the NH_2 group at 5.70 τ, thereby affording additional confirmation of structure I for the lactam.

The structure I having been fairly well established for the lactam, there remains only the necessity of explaining the conversion I → III by lead tetraacetate oxidation. If one assumes that isomerization is not involved, two fairly reasonable mechanisms for the transformation can be written. First, compounds I and VI can be considered as roughly analogous to α-amino ketones in which the α-carbon has been replaced by nitrogen. Thus, oxidation with lead tetraacetate should yield the products analogous to the acid and aldehyde expected from α-amino ketone cleavage, *i.e.*, an acid and an aryl diimide, or specifically in the case of I, *o*-carboxymethylphenyldiimide (XII). Cyclization of XII would yield III.



XII

Unfortunately, in a series of limited experiments, it has not been possible to obtain very satisfactory yields of benzene from the oxidation of VI with lead tetraacetate although, on the basis of the mechanism proposed, it would be expected that in

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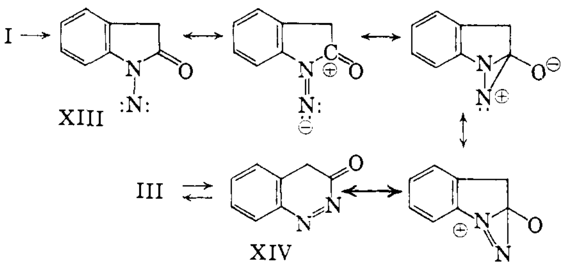
(15) E. R. Shull, J. L. Woods, J. G. Aston and D. R. Rank, *J. Chem. Phys.*, **22**, 1191 (1954).

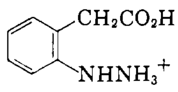
(16) The n.m.r. spectra were run by Varian Associates, Palo Alto, Calif., at a frequency of 60 mc. using deuteriochloroform as solvent, with tetramethylsilane added as an internal standard. Peak positions relative to this standard were calculated as "τ-values" (in p.p.m.) according to the recommendation of G. V. D. Tiers (*J. Phys. Chem.*, **62**, 1151 (1958); *cf.* F. A. Bovey and G. V. D. Tiers, THIS JOURNAL, **81**, 2870 (1959)). We are indebted to Mr. LeRoy Johnson of Varian Associates for an interpretation of the spectra. The interpretation is supported by the ratios of areas under the peaks cited. Thus, in the spectrum of VI the observed ratios were CH_3:NH_2, 3.0:2.0, in the spectrum of Neber's lactam CH_2:NH_2, 1.0:1.0 and in the spectrum of VII, CH_3:β-NH, 3.1:1.0 and CH_3:α-NH, 4.2:1.0. These observed ratios are exactly or very close to the ratios to be expected on the basis of the assigned structures except for that of the α-NH of VII. Since both the β-NH and CH_3 but not the α-NH group gave rise to two peaks (area ratios: β-NH, 2.7 to 1.0, and CH_3, 2.7 to 1.0, respectively) it is possible that the smaller of *two* α-NH peaks was lost under the group of peaks attributed to the ring hydrogens. It is interesting to note that the ratio of the areas of the larger peaks then would be α-NH:β-NH:CH_3, 1.0:1.0:3.1. This conclusion is not unreasonable, for in one rotational isomer of VII intramolecular hydrogen bonding involving the α-NH is possible; in the other it is not.

this case the unstable intermediate oxidation product, phenyldiimide, would break down readily to give benzene and nitrogen. On the other hand, the oxidation of N-acylphenylhydroxylamines (which might be considered to be analogous to α-hydroxy ketones) with lead tetraacetate has given moderate yields of the expected nitrosobenzenes.[17]

An alternative mechanism can be based on the speculations of Overberger, Lombardino and Hiskey,[18] who have concluded that the oxidations of *sym*-N,N-disubstituted hydrazines go through intermediates such as XIII. In their experiments with simple disubstituted hydrazines the further reaction of the intermediate involved loss of nitrogen, but in the present instance by a simple rearrangement of electrons XIII could be transformed into a tautomer (XIV) of III as shown in the equation.



With regard to the lactam itself it seems probable that it is formed from the ion XV (which, in the instance of the preparation from 3-cinnolinol, may result from the acid hydrolysis of the intermediate dihydro derivative). Protonation of the more basic β-nitrogen atom would reduce sharply the nucleophilic reactivity of that nitrogen and allow cyclization at the normally less nucleophilic α-nitrogen to form the five-ring in preference to the six-ring.



XV

The preparation of 3-cinnolinol by the oxidation of the lactam represents a new synthetic route to this type of compound. Further study will be required to determine whether or not this synthesis is of general applicability.

Experimental[19]

Neber's Lactam (1-Aminoöxindole, I). (a) Cyclization of *o*-Hydrazinophenylacetic Acid.—A solution of 20 g. (0.11 mole) of *o*-nitrophenylacetic acid[20] was prepared by neutralizing the solid acid with approximately 100 ml. of 1 *N* sodium hydroxide solution (using pHydrion paper as an indicator). The solution together with 0.5 g. of 10% palladium-on-charcoal catalyst was hydrogenated at room temperature under a hydrogen pressure of 45 p.s.i.g. The theoretical amount of hydrogen was absorbed within 1.5–3 hr. The catalyst was removed by filtration through a layer of Celite.

The solution obtained by adding 7.7 g. (0.11 mole) of sodium nitrite to the filtrate was cooled below 5° in a ice–salt-bath, and the cooled solution was added dropwise with stirring to 84 ml. of concentrated hydrochloric acid which had been cooled below 5° in the bath. Stirring was continued for 20 min. after the addition was complete, and the resulting solution of the diazonium chloride was added in small portions to a precooled (0°) solution of 75.2 g. (0.33 mole, 1.5 equiv.) of stannous chloride dihydrate in 75 ml. of concentrated hydrochloric acid. A "tin salt" began to precipitate well before the addition was complete. Following the addition the mixture was stirred for 45 min.; then it was placed in the refrigerator overnight.

The crude tin salt was collected by filtration and suspended in 200 ml. of water. The yellow solid which failed to go into solution on warming the mixture was collected and air-dried; 9 g., m.p. 108–114° (after two recrystallizations from benzene this product melted at 122–124°). The aqueous solution was saturated with hydrogen sulfide, the stannic sulfide was removed by filtration through a layer of Celite, and the filtrate was evaporated to dryness in a rotating evaporator at 40°. The residue was suspended in 80 ml. of water, and that portion which did not dissolve was collected and air-dried; 1.25 g., m.p. 120–124°. Neutralization of the filtrate with ammonium hydroxide (pHydrion paper) and chilling of the solution gave an additional 0.3 g. of product, m.p. 120–124°.

In most experiments the solids were combined at this point and recrystallized from benzene or sublimed. Recrystallization yielded 8.4–9.2 g. of chalk-white leaflets, m.p. 124–126°. Repeated recrystallization from benzene raised the m.p. to 126–128°, but elementary analysis and infrared spectral studies indicated that this material was probably a mixture of *o*-hydrazinophenylacetic acid and the cyclized product, 1-aminoöxindole. Although Neber[5] reported the isolation of the pure, free acid, in the present work no clearly authentic sample of the acid could be obtained, even when Neber's original procedure (which gave a product contaminated with stannic salts) was used.

The cyclization of the crude product could be completed by subliming the material at temperatures above 110° at 0.2 mm. pressure (above 130° at 0.5 mm.). Quantities of the crude product up to 10 g. could be handled quite easily, and the conversion was essentially quantitative, giving yields of 7.5–8.5 g. (46–52% over-all) of very pale yellow to white crystals, m.p. 125–126.5°. Alternatively, a mixture of 9.4 g. of the crude product and 150 ml. of xylene was heated under reflux for 5 hr. After cooling the solution, the solid was collected, washed with a small amount of Skellysolve B[21] and recrystallized from 250 ml. of carbon tetrachloride. 1-Aminoöxindole was collected as three crops of colorless needles totaling 7.9 g. (48% over-all), m.p. 123–127°. Recrystallization from benzene (charcoal) gave chalk-white leaflets, m.p. 126–127°, with little loss. For analysis the 1-aminoöxindole was recrystallized three times from carbon tetrachloride and once from benzene, m.p. 127.5–128°.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.56; H, 5.57; N, 19.03.

The hydrochloride was prepared by passing hydrogen chloride into a solution of 1-aminoöxindole in anhydrous ether; m.p. 185–188° dec.

Anal. Calcd. for $C_8H_9N_2OCl$: Cl, 19.21. Found: Cl, 19.45.

A 0.1-g. sample of 1-aminoöxindole was dissolved in 0.2 ml. of acetic anhydride by warming the mixture briefly. After the solution had stood at room temperature for 15 min. with occasional shaking, 5 ml. of water was added and after another 10 min. the product was collected and recrystallized from 5 ml. of water. **The 1-acetaminoöxindole** was obtained as fine, colorless needles, m.p. 190.5–192° (lit.[6] m.p. 187°), which underwent a vigorous evolution of water at 130°.

Attempts to prepare a dibenzoyl derivative by following the procedure of Neber, Knoller, Herbst and Trissler[7] gave only the monobenzoyl derivative. To an ice-cold solution of 0.50 g. (3.4 mmoles) of 1-aminoöxindole in 5 ml. of pyridine was added 0.95 g. (6.8 mmoles) of benzoyl chloride. The solution warmed noticeably and, after standing for a short time, turned red in color. After the solution had stood at room temperature for 12 hr., it was poured over 50 g. of

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(17) E. M. Miller, M.S. Thesis, University of Nebraska, April, 1959.

(18) C. G. Overberger, J. G. Lombardino and R. G. Hiskey, THIS JOURNAL, **79**, 6430 (1957).

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

(20) W. B. Wright, Jr., and K. H. Collins, THIS JOURNAL, **78**, 221 (1956).

(21) A hydrocarbon solvent, b.p. 64–69°.

crushed ice and 25 ml. of 6 *N* sulfuric acid. The solid was collected and dissolved in 50 ml. of chloroform. The chloroform solution was shaken with two 10-ml. portions of 6 *N* sulfuric acid and one of water, dried over magnesium sulfate and evaporated to dryness. The residue was recrystallized from benzene, giving 0.36 g. (42%) of **1-benzaminoöxindole**, m.p. 188–191°. Further recrystallization raised the m.p. to 192–194° (Kofler hot-stage m.p. 198.5–199°; lit.[7] m.p. for the dibenzoyl derivative, 167°; lit.[6] m.p. for the monobenzoyl derivative, 189°).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 72.41; H, 4.80; N, 11.11. Found: C, 72.33; H, 4.84; N, 11.46.

(b) **Reduction of 3-Cinnolinol.**—A mixture of 5 g. (0.034 mole) of 3-cinnolinol,[22] 5.7 g. (0.10 g. atom) of zinc dust and 200 ml. of 95% ethanol was stirred vigorously and heated to reflux and 85.5 ml. of 6 *N* sulfuric acid was added rapidly over a period of approximately 10 min. The yellow-green color of the mixture disappeared after another 10 min. and the mixture was allowed to stir an additional 20–30 min. The residual zinc was removed by filtration and washed with two 50-ml. portions of hot ethanol. The washings and filtrate were evaporated in the rotating evaporator at 40° to remove most of the ethanol. The aqueous residue was diluted with 200 ml. of water and made sufficiently basic with concentrated ammonium hydroxide to dissolve any zinc hydroxide formed. The insoluble material was collected and air-dried, giving 2.3 g. of pale yellow powder, m.p. 108–111°. The filtrate was extracted with three 200-ml. portions of chloroform and the chloroform was evaporated under reduced pressure. The pale reddish residue weighed 2.5 g. The infrared spectra of both crude products were very similar to that of purified 1-aminoöxindole and indicated the absence of any considerable amount of any other substance. The crude yields in several experiments varied from 95–99%. One recrystallization from benzene raised the m.p. to 121–123.5°, and material prepared in this way was satisfactory for most purposes. The yield at this stage was 50–76%. The product could be purified further by sublimation as described in part a above.

1-Benzalaminoöxindole.—A solution of 1.48 g. (0.01 mole) of 1-aminoöxindole and 1.06 g. (0.01 mole) of freshly distilled benzaldehyde in 20 ml. of ethanol was heated under reflux for 2 hr. on the steam-bath. The volume was reduced to approximately 15 ml. and the solution was cooled for several hours in the refrigerator. The 1-benzalaminoöxindole thus obtained weighed 2.34 g. (99%), m.p. 118–121°. A sample of analytical purity was prepared by repeated recrystallization from ethanol, m.p. 120.5–122° (lit.[6] m.p. 116°).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.29; H, 5.09; N, 11.86.

Although Neber and Keppler[6] have described a product obtained in similar fashion as 1-amino-3-benzaloxindole, the infrared spectrum of the material prepared in the present work showed no absorption in the ν(N–H) stretching region in solution (chloroform), in the Nujol mull or in the KBr wafer. The ultraviolet spectrum of the product (in 95% ethanol) was quite similar to that of 1-benzalamino-3-phenyldioxindole,[23] a compound that could have only the 1-benzalamino structure.

1-(Carbobutyoxyformal)-aminoöxindole was prepared in 83% yield by the reaction of 1-aminoöxindole and *n*-butyl glyoxalate according the procedure described for the preparation of 1-benzyl-aminoöxindole. The product formed colorless leaflets from Skellysolve B,[21] m.p. 69–70.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 65.13; H, 6.25; N, 11.24.

1-Acetamido-3-benzaloxindole.—A mixture of 1.00 g. (6.66 mmoles) of 1-aminoöxindole, 0.72 g. (6.66 mmoles) of freshly distilled benzaldehyde, 18 g. of glacial acetic acid and 2 g. of concentrated sulfuric acid was permitted to stand at room temperature for 2.5 days. The mixture was poured over 200 g. of crushed ice and allowed to stand until the ice melted. The bright yellow solid was collected and washed with water giving 1.60 g. (86%) of 1-acetamido-3-benzaloxindole, m.p. 200–212°. Further purification by recrystallization from benzene–Skellysolve B[21] raised the melting point to 228–231° (215–218° on the Kofler hot-stage).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.79; H, 5.40; N, 10.27.

o-**Aminophenylacetamide.**—The preparation of *o*-aminophenylacetamide by the reduction of *o*-nitrophenylacetamide with ferrous sulfate and aqueous ammonia has been reported by Neber, Knoller, Herbst and Trissler,[7] but two different melting points have been reported for the same acetylated derivative.

A solution of 1.80 g. (0.01 mole) of *o*-nitrophenylacetamide in 75 ml. of methanol was shaken with 0.15 g. of 10% palladized charcoal under hydrogen pressure of one atmosphere. Hydrogen absorption was rapid and the reaction was essentially complete in 6 minutes. The methanol was evaporated under reduced pressure (after removing the catalyst), and the residue was recrystallized from 50 ml. of ether (cooling in refrigerator for an extended period of time). A total of 0.97 g. (65%) of colorless needles, m.p. 106–107°, was obtained in two crops. After several further recrystallizations from benzene, the m.p. was raised to 114–115° (lit.[7] m.p. 93°).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.11; H, 6.94; N, 18.69.

The ethereal filtrates were evaporated to dryness and the residue was treated with 0.5 ml. of acetic anhydride. After standing at room temperature for 15 min., 5 ml. of water was added and the solid obtained was recrystallized from another 5 ml. of water giving 0.14 g. of *o*-**acetamidophenylacetamide** m.p. 200–203°. Further purification by recrystallization from ethanol gave fine, colorless needles, m.p. 207.5–209° (lit.[7,5] m.p. 130°, 203°).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.44; H, 6.28; N, 14.67.

Oxidation of 1-Aminoöxindole.—To a solution of 2.98 g. (0.02 mole) of 1-aminoöxindole in 100 ml. of anhydrous, thiophene-free benzene, stirred at room temperature, 8.86 g. (0.020 mole) of lead tetraacetate was added over a period of 15–30 minutes. The solution acquired a bright yellow color. Stirring was continued for 1.5–2 hr. The precipitated lead salts were separated by filtration. The solids were treated with a minimum of 6 *N* sulfuric acid and the resulting insoluble residue was separated by filtration. The aqueous solution was neutralized with sodium acetate and extracted with chloroform. Evaporation of the chloroform produced 0.42 g. of a yellow substance.

The benzene solution was evaporated to dryness in the rotating evaporator, and the residue was treated with a minimum of 6 *N* sulfuric acid. The insoluble residue was removed by filtration. The aqueous solution was neutralized with sodium acetate and extracted with chloroform. Evaporation of the chloroform produced 1.85 g. of a yellow substance. The infrared spectra of the two crude products were very nearly identical with that of authentic 3-cinnolinol (3-hydroxycinnoline). The total crude yield was 78%. The crude product could be recrystallized from benzene to yield 3-cinnolinol, m.p. 200–201°, yield 63%.

Acetyl-*unsym*-dimethylhydrazine.—To a solution of 37.9 ml. (0.5 mole) of *unsym*-dimethylhydrazine and 70 ml. (0.5 mole) of triethylamine in 10 ml. of dry carbon tetrachloride, stirred in an ice-bath, a solution of 35.3 ml. (0.5 mole) of acetyl chloride in 100 ml. of carbon tetrachloride was added dropwise at such a rate as to keep the temperature below 15°. The mixture was allowed to stand overnight in the refrigerator. The triethylamine hydrochloride was removed by filtration and the carbon tetrachloride was evaporated in the rotating evaporator. Distillation of the residual liquid gave 37 g. (73%) of colorless acetyl-*unsym*-dimethylhydrazine, b.p. 93–95° (14–16 mm.).

Anal. Calcd. for $C_4H_{10}N_2O$: C, 47.03; H, 9.87; N, 27.43. Found: C, 47.00; H, 9.65; N, 27.64.

α-Acetylphenylhydrazine (VI).—The material used in the present work was prepared in about 7.5% yield by the procedure of Behrend and Reinsberg.[24] Subsequent attempts to use this procedure gave extremely erratic results with even lower yields. The procedure of Short[25] then was employed and was found to give a product of comparable quality and better yield (30%), m.p. 125–127° (lit.[25] m.p. 125°).

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[22] W. J. Alford and K. Schofield, *J. Chem. Soc.*, 2102 (1952).

[23] The preparation of this material and pertinent ultraviolet spectra will be presented in a future communication.

[24] R. Behrend and W. Reinsberg, *Ann.*, **377**, 206 (1910).

[25] W. F. Short, *J. Chem. Soc.*, **119**, 1446 (1921).

1-Amino-3,4-dihydro-2(1H)-quinolone (IX) was prepared by the procedure of Hammick, Roe and Voaden,[26,27] m.p. 143.5–144° (lit.[26] m.p. 144°).

1-Benzalamino-3,4-dihydro-2(IH)-quinolone was prepared in 81% crude yield from the reaction of 1-amino-3,4-dihydro-2-quinolone with benzaldehyde following the procedure described above for 1-benzalaminooöxindole. The product (m.p. 91–93°) was recrystallized from ethanol, forming colorless rods, m.p. 94–95°, in 58% yield.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.10. Found: C, 76.81; H, 5.75; N, 11.01.

Benzylaldehyde α-acetylphenylhydrazone was prepared in 92% crude yield, m.p. 119–122°, by the procedure of Widman.[28] Recrystallization of the crude product from 80% ethanol gave 63% of fine, colorless needles, m.p. 120.5–122° (Kofler hot-stage m.p. 122.5–123°; lit.[27] m.p. 122°).

N-Methylacetanilide.—A solution of 3.0 g. (0.028 mole) of N-methylaniline, 3.9 ml. (0.028 mole) of triethylamine and 25 ml. of dry carbon tetrachloride was stirred and cooled below 15° while a solution of 2 ml. (0.028 mole) of acetyl chloride in 25 ml. of carbon tetrachloride was added dropwise. After the mixture had stood overnight in the refrigerator the triethylamine hydrochloride was removed by filtration and the carbon tetrachloride by flash evaporation. The white solid residue was recrystallized three times from ether, giving 2.7 g. (65%) of N-methylacetanilide as white crystals, m.p. 99–100° (lit.[29] m.p. 102°).

β-Acetyl-α-methylphenylhydrazine was prepared using a procedure like that described for N-methylacetanilide. After two recrystallizations from ether and one from benzene 8.8 g. (66%) of white crystals, m.p. 92.5–93° (lit.[30] m.p. 92–93°), was obtained from 10 g. (0.08 mole) of *unsym*-methylphenylhydrazine.

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(26) D. L. Hammick, A. M. Roe and D. J. Voaden, *Chemistry & Industry*, 251 (1954).

(27) *Cf.* S. Kruger, *ibid.*, 465 (1954).

(28) O. Widman, *Ber.*, **27**, 2964 (1894).

(29) P. Hepp, *ibid.*, **10**, 327 (1877).

(30) E. Fischer, *Ann.*, **239**, 250 (1887).

LINCOLN 8, NEBR.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Syntheses in the Colchicine Field

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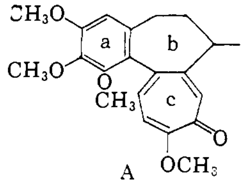
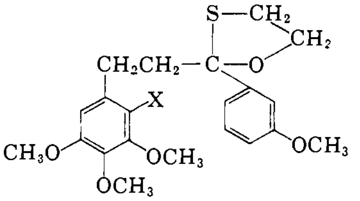
As part of a synthetic approach to colchicine the compounds 2-(3′-methoxyphenyl)-2-[β-(2″-amino-3″,4″,5″-trimethoxyphenyl)]-ethyl-1,3-dioxolane (N-2) and the corresponding oxathiolane (B-2) have been synthesized. Pschorr-type ring closure of N-2 led exclusively to 2-(3′-methoxyphenyl)-6,7,8-trimethoxyquinoline (R). The mixed anhydride (D) has been used to acylate di-*t*-butyl 3,4,5-trimethoxybenzylmalonate to give 2-methoxy-4-[α-keto-β,β-dicarbo-*t*-butoxy-γ-(3′,4′,5′-trimethoxyphenyl)]-propyltropone (C).

In an earlier publication,[3] it was suggested that colchicine (A) might be synthesized by a ring closure of the preformed "a" and "c" rings by a Pschorr cyclization. A similar approach has been investigated by Nozoe.[4] Some progress was reported[5] recently in our program by the preparation, by practical procedures, of 4-carboxytropolone and numerous derivatives.

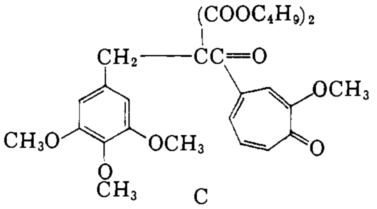


A

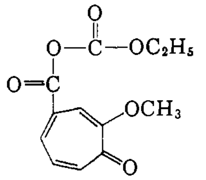


B-1, X = NO_2
2, X = NH_2
3, X = $NHCOCH_3$

The present paper describes the synthesis of the model compound B for the Pschorr cyclization, of the acyltropolone derivative C (formed *via* the crystalline carboxylic-carbonic anhydride D) and of numerous other related compounds; some of these may be useful as intermediates in a colchicine synthesis of the above type.

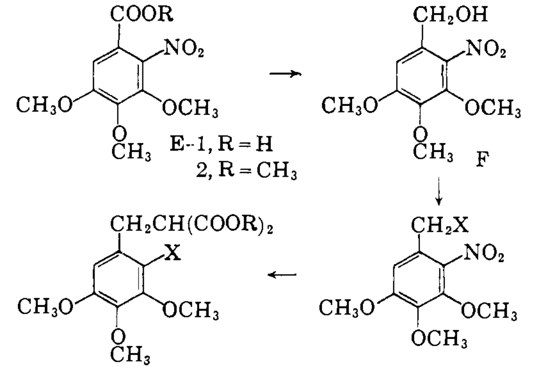


C



D

Methyl 3,4,5-trimethoxybenzoate[6] was nitrated in yields of 60% or better, with acetic anhydride–



H-1, R = *t*-C_4H_9, X = NO_2
2, R = *t*-C_4H_9, X = NH_2
3, R = *t*-C_4H_9, X = $NHCOCH_3$
4, R = *t*-C_4H_9, X = $NHCOC_6H_4OCH_3$-*m*

G-1, X = OTS
2, X = Cl
3, X = Br

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(1) Union Carbide Fellow, 1956–1957.

(2) Elon Huntington Hooker Fellow, 1956–1957.

(3) D. S. Tarbell, R. F. Smith and V. Boekelheide, THIS JOURNAL, **76**, 2470 (1954).

(4) T. Nozoe, K. Takase, Y. Kitahara and K. Doi, Abstracts of Papers Presented at the 132nd Meeting of the American Chemical Society, Sept. 8-13, 1957, p. 47. While this paper was in press, the synthesis of colchicine was reported by A. Eschenmoser, *et al.*, *Angew. Chem.*, **71**, 637 (1959), and by E. E. van Tamelen, *et al.*, THIS JOURNAL, **81**, 6341 (1959).

(5) D. S. Tarbell, K. I. H. Williams and E. J. Sehm, *ibid.*, **81**, 3443 (1959).

(6) M. T. Bogert and R. M. Isham, *ibid.*, **36**, 514 (1914).