The Interconversion of 2-(2-Aminophenyl)-3-piperolidinone and 3-(2-piperidylmethyl)-2-indolinone: A Reversible N ⇌ N′ Transacylation.

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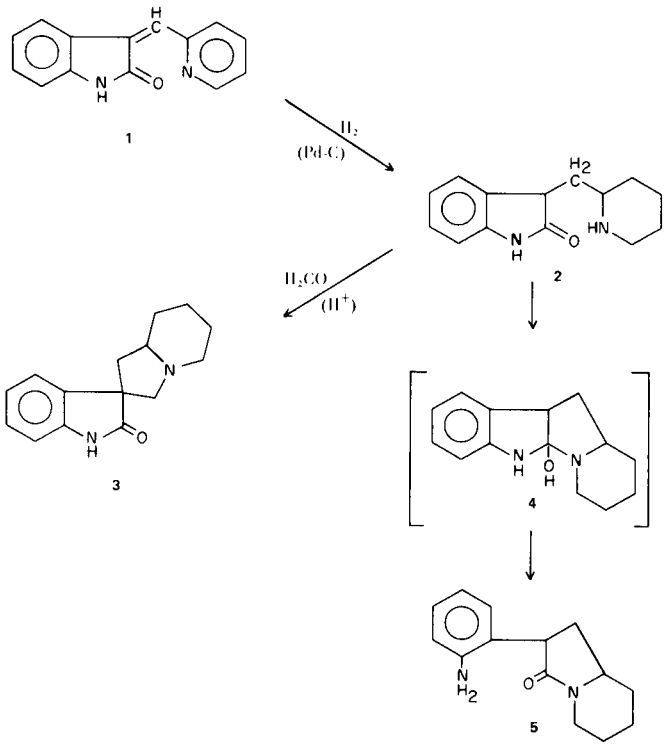
Although numerous examples of reversible O ⇌ N transacylation are cited in a review on intramolecular acyl group migration between two nucleophilic groups (2), only an abstract of a recent presentation can be found about the analogous reversible rearrangement involving acylated diamines (3). We now report the results of a study of such a reversible N ⇌ N′ transacylation (4): the interconversion of 2-(2-aminophenyl)-3-piperolidinone (**5**) and 3-(2-piperidylmethyl)-2-indolinone (2).

The N → N′ Acyl Group Migration.

3-Methyl-2-indolinone is known to undergo a facile Mannich reaction at the 3-position with formaldehyde and dimethylamine (5), and *N*-desalkyl spiro-2-indolinones have been prepared by the condensation of 3-(2-aminoethyl)-2-indolinones with aldehydes other than formaldehyde (6-9). We therefore envisioned that formaldehyde might also be used as the carbonyl component in the synthesis of *N*-desalkyl spiro-2-indolinones, and indeed, the transformation of **2** into 2-indolinone-3-spiro-2′-piperolidine (**3**) (10) (Scheme I) has been reported. However, the product **3** has not been adequately characterized (10b) and our initial attempts to accomplish this synthesis were unsuccessful. This unexpected failure prompted us to reexamine the nature of the starting material.

SCHEME I



The starting material was prepared *via* catalytic reduction of 3-(2-pyridylmethylene)-2-indolinone (**1**) in the presence of 10% palladium on charcoal at 80° in either ethyl acetate or glacial acetic acid according to the procedure of Walker *et al.* (11). The isomeric 3-(3-piperidylmethyl)- and 3-(4-piperidylmethyl)-2-indolinone were prepared similarly; however, compared to the 2-isomer, the ir and uv spectra of these two compounds were markedly dissimilar (11). The analogous mode of preparation of these 3-(piperidylmethyl)-2-indolinones and the elemental analysis data led us to believe that Walker's "3-(2-piperidylmethyl)-2-indolinone" must either: (a) have the structure **2** as assigned by Walker; or (b) be an isomeric transformation product of **2**.

Since 3-(2-aminoethyl)-2-indolinones are known to undergo facile intramolecular N → N′ transacylation (9, 12-14) to form an *o*-toluidine system, it appeared reasonable to determine if a similar rearrangement might have changed the expected reduction product **2** into its isomer **5** (15) (Scheme I). A closer examination of the synthesized product revealed: (a) an immediate positive diazotization reaction (16); (b) a similarity of its uv spectrum to that of an *o*-toluidine system (9,17); (c) the presence of a primary NH_2 doublet (λ max (chloroform) 2.94 and 3.00 μ) and the absence of a band at 3.58 μ (secondary aliphatic amine (18)) in the ir spectrum; and (d) the absence of an oxindole lactam NH absorption peak and the presence of a broadened singlet in the aromatic region (19) in the nmr spectrum. We therefore conclude that **5** must be the correct structure for Walker's compound.

The above observations indicate that the transacylation must have occurred during the hydrogenation in ethyl

acetate (20). When conducted in glacial acetic acid, however, the rearrangement must have taken place after the acetate of **2** was treated with sodium hydroxide, because the crude hydrogenation mixture (suitably diluted in acetic acid containing 10% methanol) exhibited the typical uv spectrum of oxindoles. Apparently the anticipated product **2** is stabilized against rearrangement by salt formation in acid media (21).

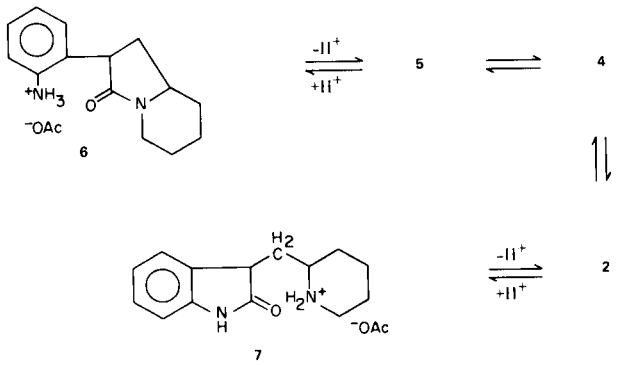
Further proof of the presence of **2** in the crude hydrogenation mixture was found when treatment of this solution with an equimolar quantity of formaldehyde resulted in the spiro-2-indolinone **3**. The structure of this condensation product was based on its characteristic mass spectral fragmentation pattern, which is very similar to that of the oxindole alkaloids (22,23). Further support is derived from its elemental analysis and absorption spectra (uv, ir, nmr) (24).

The occurrence of the transacylation of **2** in ethyl acetate in the absence of nucleophilic agents, and the failure of the isomeric 3- and 4-substituted piperidines to undergo rearrangement under similar conditions (thereby emphasizing an intramolecular steric requirement) agree with the assumption that this process proceeds through a cyclic unstable intermediate (Scheme I). Analogous mechanisms have been described for other intramolecular oxindole ring opening reactions (13,25), and for the related transacylation of *N*-(methylaminoalkyl)anilides (18). It is therefore of interest to note that the closely related isomerization of 3-(2-aminoethyl)-2-indolinone into 3-(2-aminophenyl)-2-pyrrolidone has been shown to proceed through a hydrolytic ring opening, which was followed by dehydrative ring closure (12).

The N′ → N Acyl Group Migration.

In analogy to intramolecular transacylations in which the acyl group migrates from the more nucleophilic nitrogen atom to the less nucleophilic oxygen atom, we expected to be able to utilize acidic conditions to transform **5** into the salt of the corresponding oxindole (Scheme II). This was best accomplished by dissolving **5** in either pure or slightly diluted acetic acid and leaving the solution at room temperature for 30 hours. Apparently such solvent systems are acidic enough to stabilize **2** as its salt, but are not so acidic that the less nucleophilic anilinic nitrogen in **5** becomes completely protonated. The conversion is not entirely unexpected since under acidic conditions similar intramolecular N′ → N acyl group migrations have been recorded for 3-(2-aminophenyl)-2-pyrrolidone (3), 3-(2-aminophenyl)-3-hydroxy-2-pyrrolidone (3) and 2-acetamidomethylanilines (26). It seems logical to attribute these transacylations to a favorable shift of the equilibrium (Scheme II) due to preferential protonation of the more nucleophilic nitrogen in the product. However, such a simple rationalization apparently is not applicable to all cases of acid-catalyzed *N,N′* transacylations. For example, treatment of *N*-benzoyl-*N*-phenylethylenediamine with 50% hydrogen bromide in acetic acid resulted in rearrangement products in which the less nucleophilic anilinic nitrogen became protonated. In this instance, the direction of migration is determined by the relative nucleophilicities of the two nitrogen atoms toward the acyl group (27).

Scheme II (a)



(a) The role of H^+ in the formation and transformation of the cyclic intermediate is purposefully omitted for clarity of presentation.

The course of the conversion of **5** into **7** was followed by uv, nmr spectroscopy, and tlc. Both uv (28) and nmr spectra showed a gradual development of an oxindole type spectrum which became constant after approximately 30 hours, regardless of the concentration of the reaction mixture. The surprising formation of an isosbestic point in the uv spectra, may be interpreted (30) to mean that the concentration of absorbing species other than **6** and **7** remained negligible during the rearrangement. This interpretation is supported by the thin-layer chromatograms, which, regardless of the presence or absence of methanol in the solvent, invariably showed only the same two spots, of which ultimately only the slower moving one remained. The product **7**, isolated as an amorphous powder, retained the uv and tlc characteristics of the completely rearranged solution, and appeared to be homogeneous. However, attempts at recrystallization failed, and for analytical purposes the product was converted into the hydrochloride. Structural assignment of the latter as **2** hydrochloride is fully supported by its elemental analysis and spectral (uv, ir, nmr, mass spectrum) data. It is noteworthy that all of the above observations are in agreement with the postulated intramolecular mechanism. The analytical techniques used in this study should be generally applicable to the study of reactions involving acylation and/or deacylation of anilinic nitrogen.

It would appear at first glance that the most straightforward synthesis of salts of **2** would be *via* the catalytic

hydrogenation of **1** in glacial acetic acid; however, tlc of the reduced mixture indicated that at least one major component is present in addition to **7**, and our attempts to isolate pure **7** from this mixture were unsuccessful. Rearrangement of **5**, on the other hand, though circuitous, proceeded quantitatively in glacial acetic acid (31) and must therefore be considered to be the preferred route for the preparation of salts of **2**.

EXPERIMENTAL

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Nmr spectra were obtained using a Varian A-60 A spectrometer with tetramethylsilane or Tier's salt as the internal reference; uv spectra were recorded on a Beckman DK-2A; ir spectra were taken on a Beckman IR-8; and mass spectra were measured using a RMU-7 double focusing mass spectrometer by Hitachi/Perkin Elmer. Melting points in capillary tubes were taken on a Thomas-Hoover apparatus, others were taken on a Fisher-Johns apparatus; they are not corrected. Tlc was performed on Eastman silica gel chromagram sheets with fluorescent indicator; eluants used were: 7:3 vol/vol 96% ethanol-water (solvent A), 3:1:1 wt/wt butanol-acetic acid-water (solvent B), and 4:1 vol/vol benzene-ethyl acetate (solvent C).

2-(2-Aminophenyl)-3-piperolidinone (**5**).

This compound was prepared according to the procedure given for the preparation of Walker's compound and exhibited a m.p. and uv spectrum which are in agreement with the reported values (11); ir (potassium bromide) 2.94 and 2.99 (primary NH_2), and 6.02 and 6.11 μ (amide C=O); ir (chloroform), 2.94 and 3.00 (primary NH_2), 6.01 and 6.12 (amide C=O), and no absorption at 3.58 μ (secondary aliphatic NH) (18); nmr (deuteriochloroform), δ 0.68-5.00 (m, 14, non-aromatic CH and NH_2), 6.45-7.25 (m, 4, aromatic CH), no absorption at $\delta > 7.25$ ppm; nmr (trifluoroacetic acid) δ 1.15-4.76 (m, 12, non-aromatic CH), and 7.58 ppm (broadened singlet (19), 4, aromatic CH); mass spectrum (70 eV) m/e (rel. intensity) 230 (54), 212 (21), 98 (37), 84 (100), 28 (30), 18 (22). Tlc (solvent A) showed a single spot. Diazotization reaction (32) gave a red precipitate. The compound was recovered unchanged after being heated for 0.5 hour at 250°/0.27 mm.

2-Indolinone-3-spiro-2′-piperolidine (**3**).

Hydrogenation of **1** (22.2 g., 0.10 mole) in 250 ml. of glacial acetic acid in the presence of 6 g. of 10% Pd-C at 60° for 6 hours and 42 minutes resulted in the uptake of 33 psi (0.41 mole) of hydrogen. The colorless filtrate (25 μ l diluted to 100 ml. with acetic acid) showed a typical oxindole uv spectrum with a max at 247 nm and a shoulder at 270-280 nm; tlc (solutions A and B) showed 2 major spots of which the slower moving one proved to be **7** (*vide infra*). This solution rapidly turned brown upon standing.

Half of this mixture (125 ml.) was concentrated under reduced pressure to 27.5 g., treated with 4.1 ml. (0.05 mole) of 37% formaldehyde while being stirred under nitrogen, and set aside at room temperature. After standing for 48 hours, 50 ml. of benzene and 25 ml. of acetic acid were added, and the resulting mixture was refluxed under nitrogen for 1 hour. The reaction vessel was then fitted with a Dean-Stark tube and heated for 2 hours to remove 5.8 ml. of aqueous distillate and all the benzene. The remaining dark acetic acid solution was kept at reflux temperature for another 15 minutes, cooled to room temperature, and evaporated *in vacuo* to a thick liquid. This residue was covered with 25 ml. of water and 25 ml. of chloroform, and basified with solid sodium bicarbonate. The separated aqueous phase was extracted 3 more times with 25-ml. portions of chloroform. After drying (magnesium sulfate), the combined chloroform extracts were evaporated *in vacuo* and the residue was vacuum distilled to yield 5.03 g. (41.5%) of crude **3**, a thick yellow liquid b.p. 213.5-217°/1.8-2.5 mm (frothing and decomposition). This distillate solidified spontaneously and after 3 recrystallizations from ligroin (b.p. 66-75°) afforded colorless needles, m.p. 177-181° (sealed capillary); uv (ethanol) max 249 (ϵ, 7.72 x 10^4), min 227 (ϵ, 4.11 x 10^4), and sh 273-278 nm (ϵ, 1.55 x 10^4); ir (potassium bromide), 2.92 (oxindole lactam NH), and 5.88 μ (amide C=O); nmr (deuteriochloroform) δ 0.92-3.34 (m, 13, non-aromatic CH), 6.80-7.67 (m, 4, aromatic CH), and 9.13 ppm (broadened s (19), 1, lactam NH; mass spectrum (70 eV) m/e (rel. intensity) 242 (32), 225 (2), 145 (16), 130 (9), 117 (8), 97 (100), 60 (18), 41 (14). Tlc (solution C) showed 2 spots (diastereomers).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.35; H, 7.43; N, 11.53.

3-(2-Piperidylmethyl)-2-indolinone Hydrochloride (2 hydrochloride).

In a volumetric flask was dissolved 3.56 g. (0.0155 mole) of **5** in glacial acetic acid to make 100 ml. of solution. After 48 hours at ambient temperature, the rearrangement was complete as indicated by tlc (solvent A) (*vide infra*). The clear yellow solution was acidified to Congo red by the dropwise addition of ethereal hydrochloric acid, and then evaporated *in vacuo* without heating, to give a thick yellow liquid. The residue was triturated with ether and dried overnight in a vacuum desiccator to yield 3.50 g. (84.5%) of **2**hydrochloride as a yellow powder. The product was triturated, first with boiling tetrahydrofuran, then with acetonitrile at ambient temperature, and was subsequently dissolved in absolute ethanol without heating. Addition of anhydrous ether to the filtered ethanolic solution yielded a white powder, m.p. 213-214° (prior softening and decomposition); uv (ethanol) max 249 (ϵ, 8.14 x 10^4), min 224 (ϵ, 3.27 x 10^4), and sh 275-280 nm (ϵ, 1.57 x 10^4); ir (potassium bromide) 2.95 (oxindole lactam NH) and 5.92 μ (amide C=O); nmr (deuterium oxide), δ 0.70-3.86 (m, 12, non-aromatic CH), and 7.00-7.72 ppm, (m, 4, aromatic CH); mass spectrum (70 eV) m/e (rel. intensity) 230 (13), 212 (6), 98 (32), 84 (100), 55 (10), 43 (31), 35 (14), 31 (24), 18 (8).

Tlc (solvent A) showed a single spot. This salt is unstable in hot ethanol or hot acetonitrile; attempts at recrystallization from these solvents by heating resulted in heavy losses and impure recovered material. Uv study of an ethanolic solution showed perceptible change after standing overnight at ambient temperature.

Anal. Calcd. for $C_{14}H_{19}N_2OCl$: C, 63.03; H, 7.18; N, 10.50. Found: C, 63.22; H, 7.24; N, 10.63.

3-(2-Piperidylmethyl)-2-indolinone Hydroacetate (**7**).

This compound was obtained as an amorphous homogeneous (tlc in solutions A and B) powder by trituration with ether of the residue which resulted from the evaporation (*in vacuo*, without heating) of a completely rearranged solution of **5** in acetic acid containing 10% methanol. It exhibited the typical oxindole uv spectrum. However, upon attempted recrystallization from boiling absolute ethanol only a small quantity of pure 5 (!) separated out

Rearrangement Studies (5 → 7).

Uv spectra of solutions containing 0.2 g./l. of **5** in glacial acetic acid or in acetic acid containing *ca.* 10% methanol were

recorded at various times. At these concentrations the weak absorption due to **6** cannot be seen and the gradual emergence of oxindole type spectra (with a max at the 240-250 nm region and a sh 270-280 nm) were readily observable. The spectra ceased to change after the reaction mixture had been set aside for *ca.* 30 hours at ambient temperature; when acetic acid containing 7% methanol was used as a solvent, an isosbestic point was formed at 294 nm.

Thin-layer chromatograms, developed in solvents A or B, and run concurrently with the uv spectral recordings, showed the transformation of an initially single spot into a slower moving one. Solvent B effected slow rearrangement of **5** on the absorbent; thin-layer chromatograms eluted with this solvent showed tailing of the faster moving spot. After *ca.* 30 hours standing, tlc of the reaction mixture showed only the slower moving spot; this component proved to be identical (by R_f value and by mixed tlc) with the slower moving component in the tlc of the catalytically reduced mixture of **1** in glacial acetic acid. Neither uv nor tlc measurements showed differences in the rate of change of **5** when reaction mixtures containing varying concentrations were compared.

Nmr studies of solutions containing *ca.* 10% of **5** in perdeuterioacetic acid showed (a) transfiguration of a broadened single (19) at δ 7.23 into a multiplet (b) disappearance of absorption bands between δ 4.00-4.43 ppm, and (c) emergence of a broad peak at δ 1.83 ppm. After 24 hours at ambient temperature, the sample showed no further changes in its nmr spectrum; the final spectrum was very similar but not identical to the nmr spectrum of 2 hydrochloride in perdeuterioacetic acid. On the other hand, a solution of **5** in trifluoroacetic acid showed no change in nmr spectral absorption after 4 days at ambient temperature. In this instance the spectrum resembled the nmr spectrum of a freshly prepared solution of **5** in perdeuterioacetic acid; it exhibited a broadened singlet (19) in the aromatic region.

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(14) In their long abstracts, Petracek and Yoshimura (3) reported that the transformation of 3-(2-aminoethyl)-2-indolinone is too slow to be a practical preparation of 3-(2-aminophenyl)-2-pyrrolidone.

(15) After this manuscript was ready to be submitted for publication, we learned that Petracek and Yoshimura have synthesized a compound of this structure *via* a different route. These authors noted that this compound was incorrectly identified by Walker *et al.* (11) as the isomeric oxindole **2**. Their long abstract also mentioned the possibility of converting **5** into **2** on treatment at low *p*H's.

(16) 3-(2-Aminoethyl)-2-indolinone gave a negative reaction without previous base-treatment (12).

(17) In spite of the similarity of the uv spectra of 2-indolinones and *o*-toluidine derivatives (12), we have found uv spectroscopy to be a convenient tool to distinguish between these two classes of compounds, provided the spectra are obtained in an acidic solvent. Because of the major changes in absorption characteristics that toluidines undergo upon protonation, the resulting spectra become clearly different.

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