not readily be purified further and was used as such in the next experiment. For analytical purposes, the hydrochloride of III was prepared by dissolving 30 mg. of the pure diester II in 5 ml. of boiling 6*N* hydrochloric acid and concentrating the solution to dryness. The crystalline residue melted at 288–290°.

Anal. Calcd. for $C_{17}H_{11}N_2O_4Cl$: C, 59.57; H, 3.24; N, 8.17. Found: C, 59.88; H, 3.51; N, 8.39.

2-Phenyl-1-azacycl[3.2.2]azine (IV). A mixture of 150 mg. of III and 115 mg. of copper chromite catalyst in 30 ml. of diphenyl ether was boiled under reflux for 8 hr. The solution was then diluted with benzene and the catalyst was removed by filtration. The filtrate was extracted several times with 6*N* hydrochloric acid. After neutralization, the aqueous acid extract was extracted in turn with an ether-benzene mixture. Concentration of the organic layer gave 107 mg. (100%) of yellow-orange crystals, m.p. 73–79°. These, on sublimation gave 77 mg. (72%) of pale yellow crystals; m.p. 83–84°; ultraviolet absorption (log ϵ) in neutral ethanol: 395 (4.32), 380 (4.18), 312 (4.24), 251 (4.48), 232 (4.28) and 209 mμ (4.30); ultraviolet absorption (log ϵ) in acidic ethanol (saturated with gaseous hydrogen chloride): 388 (4.32), 370 (4.39), 301 (3.99), 255 (4.45), 235 (4.19) and 212 mμ (4.48).

Anal. Calcd. for $C_{15}H_{10}N_2$: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.90; H, 4.87; N, 12.86.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS INC.]

3-Aminomethylindoles and 2-(3-Indolyl)oxazolidines from Indole-3-aldimines. Some Observations on the Acetylation of Schiff Bases

GORDON N. WALKER AND MIRIAM ANN MOORE[1]

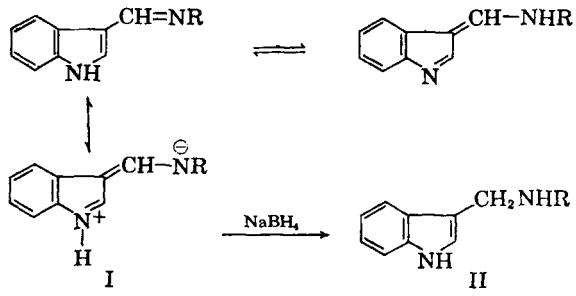
Received May 23, 1960

Sodium borohydride reduction of imines prepared from indole-3-carboxaldehyde and primary amines affords a practical synthesis of 3-alkylaminomethylindoles. Imines derived from the same aldehyde and ethanolamines undergo simultaneous acetylation and ring closure with acetic anhydride, giving 1-acetyl-2-(1-acetyl-3-indolyl)oxazolidines. This ring closure is contrasted with acetylation of certain other β-hydroxyimines in which similar oxazolidine formation does not occur, and the implications of the reaction in the special case of 3-acylindole derivatives are discussed briefly.

The appearance of several recent reports[2,3] concerning the chemistry of 3- acylindoles and corresponding indole-3-carbinols, derived from them by sodium borohydride reduction, prompts us to describe some work along similar lines which has been carried out in this laboratory during the past two years.

We became interested in aminomethylindoles for several reasons. It appeared to us that while the preparation of compounds basically related to tryptamine currently is undergoing exhaustive development in the hands of numerous investigators, little or no attention has been focused recently upon compounds related to gramine, which, pharmacologically, is interesting in its own right. Although some tertiary amines closely related to gramine have been prepared,[4] few, if any, secondary amines of the same type have been reported. Gramine and its quaternary salts have been employed frequently as synthetic intermediates ever since their now well known utility in alkylation reactions was demonstrated by Snyder[5] and his colleagues, but the field comprised of analogs of gramine has remained little exploited. Therefore we set about synthesizing a series of N_b-substituted 3-aminomethylindoles, hoping to find some representatives of this class of compounds which would have useful pharmacological properties.

It is now known that Schiff bases derived from aromatic aldehydes are reduced to secondary amines with sodium borohydride.[6] We have investigated the use of this procedure with a variety of aldimines, and we find that it is almost universally applicable whenever the products obtained are stable under alkaline conditions. Furthermore, with methanol as the solvent as directed,[6] even those secondary amines which are very sensitive to hydrogenolysis under the conditions of catalytic hydrogenation undergo a minimum of this undesirable cleavage. In the particular case at hand, the most practical approach at present to synthesis of compounds of general structure II is found to



I II

(1) Mrs. Edwin L. Klett.

(2) E. Leete, *J. Am. Chem. Soc.*, 81, 6023 (1959).

(3) J. Szmuszkowicz, *J. Am. Chem. Soc.*, 82, 1180 (1960).

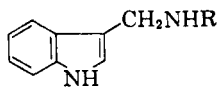
(4) See P. L. Julian, "The Chemistry of Indoles," Chap. 1, in Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1952, Vol. 3, p. 54, for a summary of some gramine analogs prepared by the usual Mannich condensation.

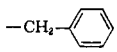
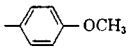
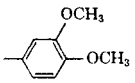
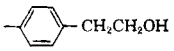
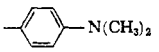
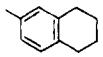
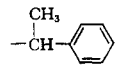
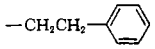
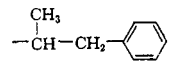
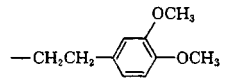
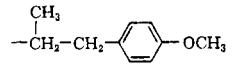
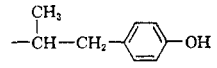
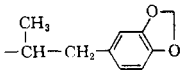
(5) H. R. Snyder, *et al.*, *J. Am. Chem. Soc.*, 66, 200 (1944); 70, 1857, 3770 (1948); 71, 663 (1949). See also Ref. 4.

(6) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, 22, 1068 (1957).

TABLE I

SECONDARY AMINES



R	Empirical Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	$C_{15}H_{20}N_2$	90	115	78.9	8.8	12.3	78.8	9.0	12.6
	$C_{16}H_{16}N_2$	78	95	81.3	6.8	11.9	81.4	6.8	11.7
	$C_{16}H_{18}ON_2$	87	110	76.2	6.4	11.1	75.9	6.3	10.9
	$C_{17}H_{18}O_2N_2$	65	106	72.3	6.4	9.92	72.5	6.5	9.79
	$C_{17}H_{18}ON_2$	80	96	76.6	6.8	10.5	76.6	6.7	10.6
	$C_{17}H_{19}N_3$	58	131	76.9	7.2	15.8	77.0	7.4	15.8
	$C_{19}H_{20}N_2$	55	107	82.6	7.3	10.1	82.6	7.2	10.2
	$C_{17}H_{18}N_2$	67	101	81.6	7.3	11.2	81.5	7.2	11.5
	$C_{17}H_{18}N_2 \cdot HCl$[a]	45	169 dec.	71.2	6.7	9.77	71.2	6.8	9.65
	$C_{18}H_{20}N_2 \cdot HCl$[a]	26	155 dec.	71.9	7.0	9.31	71.6	7.1	9.50
	$C_{19}H_{22}O_2N_2 \cdot HCl$[a]	90	176 dec.	65.8	6.7	8.07	65.8	6.9	7.74
	$C_{19}H_{22}ON_2 \cdot HCl$[a,b]	38	164 dec.	69.0	7.0	8.47	69.4	7.0	8.26
	$C_{18}H_{20}ON_2 \cdot HCl$[a]	35	170 dec.	68.2	6.7	8.84	67.5	6.8	8.64
	$C_{19}H_{20}O_2N_2 \cdot HCl \cdot 3^1/_2H_2O$	31	182 dec.	56.0	6.9	6.87	55.8	6.7	6.73

[a] Light-sensitive. [b] Hygroscopic.

consist of sodium borohydride reduction of indole-3-aldimines (I), which parallels the similar reduction of 3-indolealdehydes[2] and ketones[3] to corresponding carbinols. Secondary amines which were prepared in this way are listed in Table I. In instances where the amines obtained were not crystalline, the most conveniently prepared derivative was the hydrochloride, even though many of the amines, as might be expected by analogy with 3-hydroxymethylindoles,[2] are rather acid-sensitive.[7]

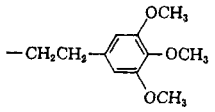
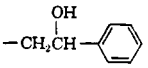
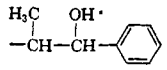
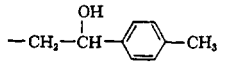
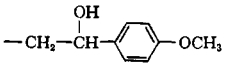
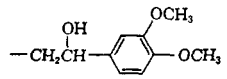
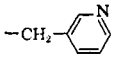
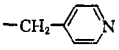
We observed that the sodium borohydride reduction of compounds I was consistently rather sluggish in comparison with reduction of other, more typical, aromatic aldimines[6] by the same procedure. This may be attributed to the partial (vinylogous) amidine character of imines I, perhaps best expressed as shown in the formulas; the double bond which is attacked in this reaction is to some extent hybridized, or delocalized. The partial amide-like nature of indole- and pyrrole-carboxaldehydes and ketones has been commented upon previously[8,9] and currently partial-zwitterionic structures, in addition to the older, tautomeric representations,

(7) The acid-lability of these compounds may explain our lack of success in attempts to carry out Eschweiler-Clarke *N*-methylation with some of the secondary amines. Alternatively, alkylations under either acidic or basic conditions may suffer from interference by competitive reaction at the indole nitrogen.

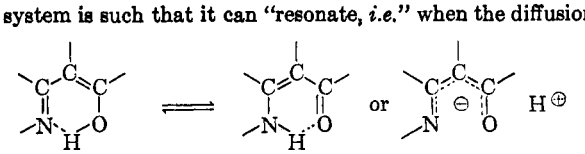
(8) J. Thesing, *Ber.*, **87**, 507 (1954).

(9) W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958).

TABLE I (*Continued*)

	Empirical Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	$C_{20}H_{24}O_3N_2 \cdot HCl$	42	159	63.8	6.7	7.4	63.1	6.9	7.2
	$C_{17}H_{18}ON_2$	27	148	76.7	6.8	10.5	76.8	7.15	10.3
	$C_{18}H_{20}ON_2$[b]	30	116	77.1	7.2	9.99	77.1	7.3	9.76
	$C_{18}H_{20}ON_2$	87	165	77.1	7.2	9.99	77.4	7.4	9.82
	$C_{18}H_{20}O_2N_2$	80	149	73.0	6.8	9.45	72.3	6.8	9.22
	$C_{19}H_{22}O_3N_2$	25	97	69.9	6.8	8.6	68.6	6.8	8.2
	$C_{14}H_{12}N_2$	19	109	75.3	5.9	18.8	75.4	6.0	18.7
	$C_{14}H_{12}N_2$	95	133	75.3	5.9	18.8	75.2	5.8	19.1
	$C_{15}H_{15}N_3 \cdot 2HCl$[a,b]	55	220 dec.	58.0	5.5	13.5	57.8	5.8	13.3
	$C_{15}H_{15}N_3 \cdot 2HCl$[b]	51	171 dec.	58.0	5.5	13.5	—	—	13.6
	$C_{12}H_{11}N_3S$	88	140	62.9	4.8	18.3	62.7	4.7	18.2
	$C_{16}H_{13}N_3S$	78	186	68.8	4.7	15.1	68.9	4.8	15.2
$-CH_2CH_2N(C_2H_5)_2$	$C_{15}H_{22}N_2 \cdot 2HCl$	53	157 dec.	56.6	7.9	13.2	56.1	7.9	13.4
$-CH_2CH_2CH_2N(CH_3)_2$	$C_{14}H_{21}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	26	163 dec.	53.7	7.7	13.4	53.7	7.7	13.5
	$C_{14}H_{19}N_3 \cdot 2HCl$	75	*ca.* 150 dec.	55.6	7.0	13.9	55.6	7.3	13.9
	$C_{15}H_{21}N_3 \cdot 2HCl$	10	202 dec.	57.0	7.3	13.3	56.8	7.5	13.4
	$C_{14}H_{20}N_4$	100	173	68.8	8.3	22.9	69.1	8.2	22.6

have been invoked[9] to account for the observed properties of these compounds. Actually they may be regarded as special (cyclic) cases of a conceivably general class of 1,3-iminocarbonyl compounds; *i.e.*, nitrogen analogs of the better known 1,3-dicarbonyl compounds[10] and 1,3-diimines derived also J. Weinstein and G. M. Wyman, *J. Org. Chem.*, 23, 1618 (1958), for discussion of some hybrid systems of this type in the light of spectral data. Such compounds *id genus omni*, are marked by unusual infrared spectra, in which no carbonyl band is seen where it would normally appear, were it not for the presence of the additional group, and "zwitterionic" bands are also sometimes observed when the system is such that it can "resonate, *i.e.*" when the diffusion

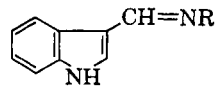


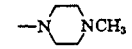
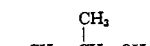
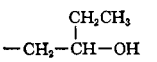
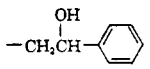
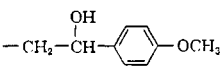
of double and single bonds results in a mesomeric hydrogen atom.

(10) Just as it is usually difficult or impossible to distinguish chemically the subtle difference between tautomers of 1,3-diketones, so it is also rather meaningless to attempt to specify exact locations of double bonds and/or protons in 1,3-iminocarbonyl- or diimino systems; these probably are different in most cases depending upon whether the compound is in the solid state or in solution. See N. H. Cromwell, *et al.*, *J. Am. Chem. Soc.*, 71, 3337 (1941), and

TABLE II

INDOLE-3-ALDIMINES



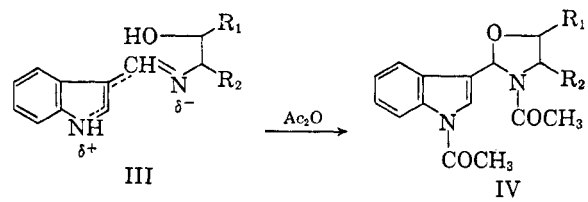
R	Empirical Formula	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-N(CH_3)_2$	$C_{11}H_{13}N_3$	105[a]	70.6	7.0	22.4	70.8	7.1	22.5
	$C_{14}H_{18}N_4$	175[b]	69.4	7.5	23.1	69.7	7.4	23.4
$-CH_2CH_2OH$	$C_{11}H_{12}ON_2$	136[c,d]	70.2	6.4	14.9	70.3	6.4	14.8
	$C_{12}H_{14}ON_2$	104[c,e]	71.26	7.0	13.9	71.04	7.0	13.9
	$C_{13}H_{16}ON_2$	169[c,e]	72.2	7.5	13.0	72.0	7.4	12.8
	$C_{17}H_{16}ON_2$	165[c,d]	77.3	6.1	10.6	77.4	6.3	10.4
	$C_{18}H_{18}O_2N$	159[c,e]	73.45	6.2	9.52	73.13	6.3	9.50

Recrystallized from [a] cyclohexane–ethyl acetate, [b] methanol, [c] ethyl acetate, [d] Infrared peak at 6.10 μ, [e] Infrared peak at 6.08 μ.

from such iminocarbonyl compounds can be expected to reflect the hybrid nature of the parent substances.

Because of the relative sparsity of information about the chemical behavior of 1,3-diimino compounds, we were intrigued in finding a novel acetylation and ring closure with imines derived from indole-3-aldehyde and ethanolamines, which lent added credibility to the concept of labile double bonds, such as shown in I, since the reaction, *ut infra*, obviously had to depend upon a genuine delocalization of conjugated double bonds within the system.

Included among the indole-3-aldimines which we prepared were some compounds III derived from *o*-aminophenol and aliphatic β-hydroxyamines (see Table II). We had noticed that these compounds were unusual in comparison with the other imines, being colorless and having good crystalline properties, as well as being stable to boiling alcohols. The suspicion that they might be oxazolidines, rather than hydroxyimines, was, however, allayed by observation of the infrared spectra, which showed both conjugated imine or eneamine (6.08–6.10 μ) and bonded OH (3.14 μ) bands; similar formation of hydroxyimines, rather than oxazolidines, from *p*-dialkylaminobenzaldehydes and ethanolamines has been observed recently,[11] and there is good agreement between the spectral data presented for those compounds and the infrared bands which we observed in III. Furthermore we were able to reduce most of the hydroxyimines with sodium borohydride, to corresponding hydroxyamines (included in Table I). When the compounds (III) were treated with acetic anhydride, simultaneous acetylation of both nitrogen atoms and ring closure to the oxazolidines IV occurred, the reaction taking place very readily, in some cases even exothermically (notably when $R_1 = R_2 = H$). The properties of compounds IV, obtained in this way, are recorded in Table III.



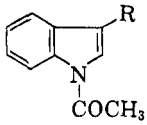
III IV

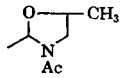
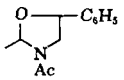
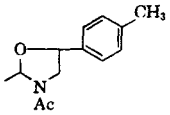
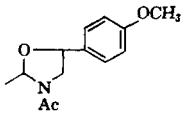
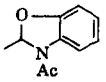
Their infrared spectra provided good evidence for structure IV, showing clearly both N_a-acetyl (5.8–5.85 μ) and N_b-acetyl (6.02–6.07 μ) peaks in the expected regions, as well as the usual aromatic band (*ca.* 6.20 μ) and also the triplet in the 1080–1200 cm.$^{-1}$ region which has been ascribed[11] to oxazolidine O—C—N. That no cyclization involving the 2- or 3-positions of the indole ring had occurred was evidenced by the fact that compound IV ($R_1 = R_2 = H$) was hydrolyzed and cleaved readily with hot, dilute alkali or with acids, to give indole-3-aldehyde, and also by the preparation of the homologous and quite similar oxazine, starting with 3-aminopropanol in place of ethanol-

(11) M. Nakamichi and G. L. Webster, *J. Org. Chem.*, 22, 159 (1957). We believe that the bonding of the hydroxyl group is intermolecular, rather than a chelating effect.

TABLE III

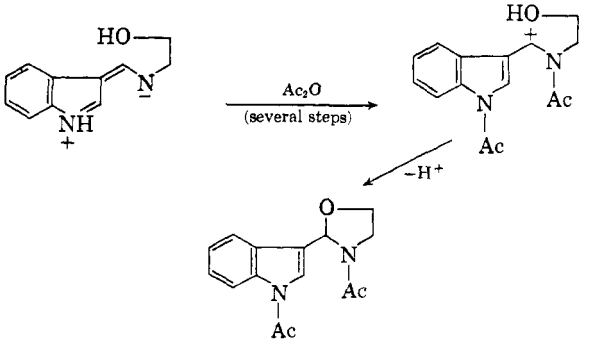
ACETYLOXAZOLIDINES AND RELATED COMPOUNDS



R	Empirical Formula	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Infrared, μ Max. (Nujol) N_a-Ac	Infrared, μ Max. (Nujol) N_b-Ac
	$C_{15}H_{16}O_3N_2$	157	66.16	5.92	10.3	65.9	5.92	10.3	5.84	6.05
	$C_{16}H_{18}O_3N_2$	169	67.11	6.34	9.78	67.04	6.43	9.76	5.81	6.02
	$C_{21}H_{20}O_3N_2$	157	72.39	5.79	8.04	72.64	6.05	8.32	5.80	6.06
	$C_{22}H_{22}O_3N_2$	157	72.91	6.12	7.73	72.86	6.28	7.54	5.79	6.07
	$C_{22}H_{22}O_4N_2$	105	69.82	5.86	7.40	69.57	5.89	7.17	5.84	6.02
	$C_{19}H_{16}O_3N_2$	179	71.24	5.03	8.75	70.75	5.04	8.52	5.82	6.03
	$C_{16}H_{18}O_3N_2$	194	67.11	6.34	9.78	67.24	6.31	9.50	5.86	6.04

amine.[12] Finally further evidence for structures III and IV was adduced from the ultraviolet spectra,[13] which showed the change from the conjugated indoleimine III to the more typical indole chromophore of IV.[13]

The process of conversion of III to IV with acetic anhydride takes place very smoothly, which is in sharp contrast to the difficulty usually experienced in 1-acetylation of simple indoles. In our view, this ease of reaction is due to the fact that acetic anhydride interacts initially, in a 1,4-manner, with the delocalized, conjugated indoleimine system, forming *N*-acetyl derivative(s) in which a carbonium ion, or reactive acetoxy group, is left upon the carbon next to position 3 of the indole ring, and that this intermediate then undergoes rapid cyclization *via* attack by the hydroxyl group. The process may be visualized as occurring in several alternative ways, all with the same net result:

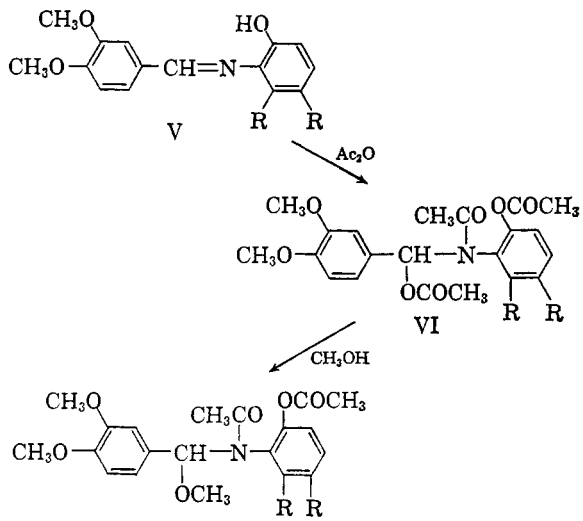


It seems rather pointless to argue the question of which nitrogen is attacked first, since indeed they may be affected simultaneously. In any event it is clear that the reaction proceeds smoothly to completion because there is present a hydroxyl group, the hydrogen of which can capture the moiety present on the (formerly aldehydic) carbon, since no such smooth reaction with acetic anhydride is experienced with simpler aldimines, indolic or otherwise, in which a β-hydroxyl

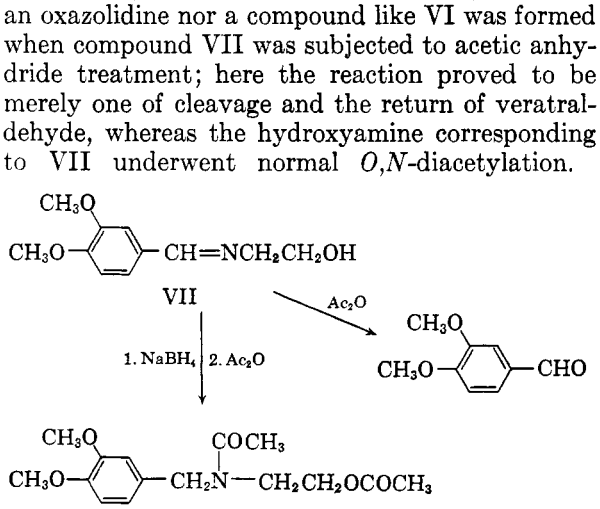
(12) Cyclization of 3-indolyl—CH=N$(CH_2)_3$OH at the 2- or 3-position of the indole ring would involve the very unlikely formation, respectively, of 8- or 7-membered ring compounds.

(13) The following ultraviolet maxima in alcohol were observed, where $R_1 = R_2 = H$: for III, 259 and 292 mμ (log ε 4.08 and 4.09, respectively); for IV, 238, 289 and 298 mμ (log ε 4.19, 3.75 and 3.785, respectively).

group is not present. It is instructive to compare this reaction with the change which takes place when acetic anhydride acts upon imines (V) derived from *o*-aminophenols and veratraldehyde, an aldehyde which is not capable of mesohydric or partial zwitterionic hybridization. Veratraldehyde was chosen for these model reactions because of the good crystalline properties of 3,4-dimethoxyphenyl compounds. The product in these cases is



not an *N*-acetyloxazolidine, but merely VI, a fully acetylated version of the Schiff base. Evidently the attack of acetic anhydride upon C=N of a non-hybridized, ordinary aldimine is slower than its reaction with the C=N group when that moiety is one of two components of a 1,3-diimino-system, thus allowing acetylation of the hydroxyl group to intervene. This interpretation seems more likely to be correct than the alternative one, namely than an oxazolidine is formed first from V and subsequently is re-opened by acetic anhydride, and this reasoning is to some extent bolstered by two further observations: (1) Neither an oxazolidine nor a compound like VI was formed when compound VII was subjected to acetic anhydride treatment; here the reaction proved to be merely one of cleavage and the return of veratraldehyde, whereas the hydroxyamine corresponding to VII underwent normal *O,N*-diacetylation.



(2) Evidence was found (see Experimental) that there is no lack of reactivity of the (formerly aldehydic) —CH—OAc in compounds such as VI, which in certain instances react readily with water or alcohols. This lends weight to the idea that acetylation of the phenolic hydroxyl group takes place before the reactive —CH(OAc)—NAc— group is formed.

NOTE ADDED IN PROOF: The addition of acetic anhydride to anils and other less stable Schiff bases has already been investigated to some extent: see J. B. Ekely, M. C. Swisher and C. C. Johnson, *Gazz. chim. ital.*, **62**, 81 (1932), and H. Breederveld, *Rec. Trav. chim.*, **79**, 401 (1960).

Whatever precise mechanisms or order of events may be involved in acetylation of imines, we suggest that the sequence of reactions, first with a β-hydroxyamine and then with acetic anhydride, may be generally useful in preparing crystalline derivatives from, and gaining some diagnostic information about, other β-iminocarbonyl compounds in addition to the type studied here.

EXPERIMENTAL[14]

Materials. The amines used as starting materials were purchased from various commercial sources, with the exception of the following: 1-(*p*-hydroxyphenyl)-2-aminopropane was prepared by hydrogen bromide cleavage of the corresponding methyl ether; 1-(*p*-methoxyphenyl)-2-aminoethanol, 1-(3,4-dimethoxyphenyl)-2-aminoethanol, and 1-(*p*-methylphenyl)-2-aminoethanol were synthesized from the corresponding phenacyl bromides *via* hexamethylenetetramine salts,[15] hydrochloric acid cleavage[15] to aminoketone hydrochlorides, and subsequent reduction in the presence of palladium-charcoal, an approach which we found to be considerably more reliable and more easily carried out than similar reduction of nitrosoketones.[16] 3-Aminopiperidine was prepared by platinum-catalyzed reduction of 3-aminopyridine hydrochloride,[17] and 1-methyl-4-aminopiperidine by sodium borohydride reduction of 1-methyl-4-aminopyridinium iodide.[18] 1-Methyl-4-aminopiperazine was prepared by zinc–acetic acid reduction of 1-methyl-4-nitrosopiperazine.[19] Indole-3-aldehyde was purchased from Aldrich Chemical Company.

General procedure in preparation of indole-3-aldimines (I). The compounds used as precursors of the amines listed in Table I, some of which were characterized (Table II) as such, were prepared by the well known azeotropic method, as follows: A solution of from 5 to 15 g. of indole-3-aldehyde and 1.02 equivalents of the appropriate amine, in 200–400 ml. of toluene was refluxed under a water-separator for as long as was required to collect *ca.* the theoretical amount of water. The time required varied from 2 to 12 hr., depending upon the basicity of the amine. With some of the slower reactions it occasionally seemed helpful to stop the refluxing, let the solution stand overnight at room temperature, and resume refluxing the next morning, when additional water usually appeared. The hot solution was filtered, or often conveniently decanted, free of any insoluble residue present, and was evaporated to dryness on the steam bath. The crude imines thus obtained were oils in some cases, crystalline in others, but in neither event was it necessary or advisable to attempt to purify them before going ahead with

(14) Melting points are corrected.

(15) The method of C. Mannich and F. L. Hahn, *Ber.*, **28**, 1542 (1911).

(16) See W. H. Hartung and J. C. Munch, *J. Am. Chem. Soc.*, **51**, 2262 (1929).

(17) H. Nienburg, *Ber.*, **70B**, 635 (1937).

(18) *Cf.* K. Tomita, *Chem. Abstr.*, **46**, 5044; **48**, 10020[a].

(19) E. A. Conroy, U. S. Patent **2,663,706** (1953).

reduction. A quantitative yield of imine was assumed when approximately the expected amount of water had been trapped during the reaction, and the yields of compounds listed in Table I are over-all yields for the two-stage process, based upon the amount of indole-3-aldehyde used at the start.

In a few cases, notably 3-aminopyridine, when the reaction was very slow in toluene, this solvent was replaced with xylene in order to speed the reaction.

General procedure in reduction of imines to amines (II). A solution or suspension of 10 g. of the imine in 100–200 ml. of methanol was treated with *ca.* 20 g. of sodium borohydride in portions, and the mixture, after subsidence of any initial vigorous effervescence, was heated on the steam bath for 0.5–1 hr., with occasional stirring, until the reagent was consumed and until most of the methanol had boiled away. When the reaction was obviously very slow, additional sodium borohydride, and more methanol when required, were added in portions, during the heating period. It was possible, after some experience, to tell when the reduction was complete by gauging the vigor or lack of vigor, of the effervescence produced by further addition of sodium borohydride to the mixture. The concentrated reaction mixture was cooled and treated with 100–200 ml. of water. If the product crystallized at this point it was collected, washed with water, and dried. If the material did not crystallize, it was extracted with 500 ml. of ether, after the addition of enough sodium chloride to saturate the aqueous layer. The ether solution was dried over anhydrous potassium carbonate and evaporated. If the amine crystallized it was triturated with a small quantity of ether and dried. Noncrystalline amines were converted to hydrochlorides using ethanolic hydrogen chloride, and the products were precipitated, if necessary, in the initial preparation and in subsequent recrystallization (ethanol) by the addition of enough dry ether to produce turbidity. Every effort was made to isolate and purify hydrochlorides as rapidly as possible, in order to avoid decomposition in the presence of excess hydrogen chloride. The occasional low yield values in Table I usually reflect losses on account of difficulty in isolation and purification of poorly crystallized or unstable compounds, rather than any shortcoming of the borohydride reaction.

The *N*,*N*-dimethylhydrazone (first compound in Table II) and the phenylhydrazone of indole-3-aldehyde were not reduced appreciably by sodium borohydride in methanol, even though the reaction time was prolonged to 8 hr. The ethanolamine derivative (third compound in Table II) apparently was reduced, but neither the amine which was formed, nor its hydrochloride or picrate could be obtained in crystalline form; the latter derivatives were unstable.

General procedure in acetylation of hydroxyamines (III) *to* IV. The hydroxyimine (5 g.) was treated with 100 ml. of acetic anhydride, whereupon in most instances an exothermic effect was noticed and the material dissolved, giving a yellow solution. The solution was refluxed for 0.5–1 hr., and the excess acetic anhydride was evaporated. The residue crystallized either immediately or after the addition of a little ethyl acetate. The crystals were triturated with ethyl acetate, in some instances with added cyclohexane, and were recrystallized using the same solvents. The products (see Table III) were obtained in yields of 70–85% with the exception of the sixth example (the *o*-aminophenol derivative) where the yield was *ca.* 10%, and the last example (oxazine) where the yield was virtually quantitative.

Hydrolysis of compound IV ($R_1 = R_2 = H$). A mixture of 1.6 g. of the diacetyloxazolidine and 45 ml. of 5% sodium hydroxide solution was brought to boiling and kept at the boiling point for 1 min. The crystals dissolved rapidly. Upon cooling the solution, crystals (0.6 g.) of indole-3-aldehyde separated which, after being washed with water and recrystallized from ethyl acetate, had m.p. 196–198°, undepressed upon admixture with an authentic specimen. The infrared spectrum was identical with that of indole-3-aldehyde.

The same hydrolysis product was also obtained when a sample of IV ($R_1 = R_2 = H$) was allowed to stand with excess 1:1 hydrochloric acid at room temperature for 0.5 hr. and the solution subsequently treated at room temperature with sodium hydroxide solution.

Compound V ($R = H$) *and acetylation to form VI* ($R = H$). (A). A solution of 27 g. of veratraldehyde and 17.6 g. of *o*-aminophenol in 300 ml. of benzene was refluxed under a water-separator for 1.5 hr., by which time the expected quantity of water had been collected. The hot solution was filtered, and the solution was evaporated to a volume of *ca.* 100 ml., cooled, and treated with cyclohexane until crystallization began. The product was collected, after it had crystallized completely at ice temperature, and was washed with cyclohexanebenzene (2:1). The yield of tan or grey crystals, m.p. 99–100°, was 41 g. Recrystallization from cyclohexane–ethyl acetate gave pale yellow crystals, m.p. 100—102°, which gave a pronounced ferric chloride test.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.0; H, 5.9; N, 5.4. Found: C, 69.8; H, 5.8; N, 5.7.

(B). *Acetylation.* A mixture of 15.4 g. of the foregoing Schiff base and 100 ml. of acetic anhydride was refluxed for 1 hr. The solution was evaporated to small volume on the steam cone; the residual red oil was cooled and treated with a little ethyl acetate. The crystals which soon formed were collected, washed with ethyl acetate, and air-dried. The yield of colorless product, m.p. 144–147°, was 8.9 g. (37%). Recrystallization from ethyl acetate raised the m.p. to 147–149°.

Anal. Calcd. for $C_{21}H_{23}O_7N$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.81; H, 5.84; N, 3.51.

The infrared spectrum (Nujol) showed peaks at 5.69, 5.81, and 5.98 μ (phenolacetate, aliphatic acetoxy, and *N*-acetyl, respectively), and there were no NH or OH bands evident. There was also no ferric chloride test.

This compound reacted with warm methanol, giving a colorless, glassy product which could not be induced to crystallize. The infrared spectrum of the material (dried *in vacuo*) showed peaks at 5.71 and 6.05 μ, indicating that the aliphatic acetoxy group had been replaced by methoxyl. More definitive results along this line were obtained with the compounds next described.

Compound V [$RR = -(CH_2)_4-$] *and acetylation to form VI* [$RR = -(CH_2)_4-$]. (A). Crude 1-amino-5,6,7,8-tetrahydro-2-naphthol,[20] prepared by catalytic reduction of 5.2 g. of α-nitroso-β-naphthol, and 5.3 g. of veratraldehyde were dissolved in 100 ml. of ethyl acetate, 6 drops of glacial acetic acid were added, and the solution was heated on the steam cone for 1 hr., while the greater part of the solvent was allowed to evaporate. The concentrated solution was cooled and scratched to induce crystallization which, once begun, was rapid and complete. The product was collected and washed with cyclohexane–ethyl acetate; yield 4.1 g. (41%) of light yellow crystals, m.p. 155–158°. Recrystallization from ethyl acetate afforded pale yellow crystals, m.p. 159–161°. The compound gave a deep red ferric chloride test.

Anal. Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.07; H, 6.60; N, 4.55.

(B). *Acetylation.* A solution of 2.1 g. of this Schiff base and 40 ml. of acetic anhydride was refluxed for 1 hr. Evaporation of the excess reagent gave a rapidly crystallizing residue which, upon immediate trituration with ethyl acetate, afforded 2.0 g. of colorless crystals, m.p. 175–177°. This melting point was not raised by recrystallization of the compound from ethyl acetate and, in fact, was lowered when a sample of the crystals was allowed to come into contact with moisture from the steam cone. The ferric chloride test was negative.

(20) *Cf.* G. Schroeter, *Ann.*, **426**, 1 (1922).

Anal. Calcd. for $C_{25}H_{29}O_7N$: C, 65.92; H, 6.42; N, 3.08. Found: C, 66.09; H, 6.23; N, 3.21.

The infrared spectrum (Nujol) showed peaks at 5.65, 5.77, and 5.99 μ, and no NH or OH absorption.

Upon treatment with warm methanol, this compound released acetic acid (Calcd. $C_2H_4O_2$, 13.2%. Found: 12.8%) and formed the compound in which *the aliphatic acetoxyl group is replaced by methoxyl*. Recrystallization of this product from cyclohexane–ethyl acetate afforded colorless, cottony crystals, m.p. 129–131°. The infrared spectrum (Nujol) showed that the phenolic acetate and *N*-acetyl groups (5.69 and 6.02 μ, respectively) were retained, while the original acetoxy (5.77 μ) peak was absent.

Anal. Calcd. for $C_{24}H_{29}O_6N$: C, 67.43; H, 6.84; N, 3.28; OCH_3, 21.8. Found: C, 67.57; H, 6.63; N, 3.35; OCH_3, 20.4.

Both this compound and its triacetate precursor were hydrolyzed by boiling with 5% sodium hydroxide solution for a few minutes to give *1-acetylamino-5,6,7,8-tetrahydro-2-naphthol;* m.p. 196–198°, after recrystallization from ethyl acetate. The compound gave a green ferric chloride test.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.33; H, 7.19; N, 6.90.

Compound VII. A solution of 20 g. of veratraldehyde and 8 g. of ethanolamine in 300 ml. of benzene was refluxed under a water-separator for 1 hr. Evaporation of the solvent, and trituration of the crystalline residue with benzene, gave 23.7 g. of colorless crystals, m.p. 102–104°. Recrystallization from ethyl acetate raised the m.p. to 104–105°.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.25; H, 7.51; N, 6.62.

Reduction of this compound with sodium borohydride in methanol by the usual procedure afforded a quantitative yield of yellow, oily *hydroxyamine*, which was characterized by preparing the *O,N-diacetate* (VIII): the oil was refluxed with excess acetic anhydride for 2 hr., and after evaporation of the reagent, the product was recrystallized from cyclohexane–ethyl acetate; colorless crystals, m.p. 91–92°.

Anal. Calcd. for $C_{15}H_{21}O_5N$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.96; H, 7.12; N, 4.74.

When 5 g. of Compound VII and 50 ml. of acetic anhydride were refluxed for 1 hr., there was isolated 1.6 g. of veratraldehyde, after careful trituration of the crude product with ethyl acetate.

Acknowledgment. It is a pleasure to thank the following members or former members of Mr. Louis Dorfman's staff for microanalytical and spectrophotometric work: Mr. George Robertson, Miss Natalie Cahoon, Miss Patricia Gallant, Mrs. Violet Loire, Miss Margaret Jones, Mrs. Vivian Scarinza, and Mr. Herbert Behrens; and Mr. Dorfman himself for interesting discussion on various aspects of spectra involved in this work. Assistance with the preparation of some of the compounds was also rendered by Misses Patricia Wenk and Barbara Weaver.

SUMMIT, N. J.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF NORTH DAKOTA AND HOFSTRA COLLEGE]

Angular-Substituted Hydrocarbazoles. I. 6-Benzenesulfonamido-4-keto-9-benzenesulfonyl-11-methyl-2,3,4,11-tetrahydrocarbazole[1,2]

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Synthesis of an angular-substituted 4-ketotetrahydrocarbazole, 6-benzenesulfonamido-4-keto-9-benzenesulfonyl-11-methyl-2,3,4,11-tetrahydrocarbazole, by the addition of active methylene compounds to quinone diimides, is described. 1,3-Cyclohexanedione, 2-methyl-1,3-cyclohexanedione, and 2-carbethoxymethyl-1,3-cyclohexanedione were added to *p*-quinonedibenzenesulfonimide and the products cyclized to indoles. The cyclohexanedione ring in the adducts was cleaved by heating with acetic acid and indoles were formed. Dilute alkali also induced cleavage of the cyclohexanedione ring, with formation of indoles. Acetic anhydride in pyridine cyclized the adduct from 2-methyl-1,3-cyclohexanedione and *p*-quinonedibenzenesulfonimide to the *N*-acetyl derivative of 6-benzenesulfonamido-4-keto-9-benzenesulfonyl-11-methyl-2,3,4,11-tetrahydrocarbazole, without ring cleavage; but with 2-(2,5-dibenzenesulfonamidophenyl)-2-carbethoxymethylcyclohexane-1,3-dione acetic anhydride gave a carbostyril, which appears to be the preferred course when such a mode of cyclization is possible.

Although the total synthesis of strychnine has been accomplished,[3] a search for simpler routes to strychnine-like substances is still desirable. The present paper describes the synthesis of an angular-substituted hydrocarbazole of interest in connection with the synthesis of substances related to strychnine.

Adams and Blomstrom[4] found that *p*-quinonedibenzenesulfonimide would add active methylene compounds in the presence of catalytic amounts of sodium methoxide, and Adams and Samuels[5] developed an excellent indole synthesis based upon cyclization of these adducts. It occurred to the present authors that a similar series of reactions applied to a 2-substituted 1,3-cyclohexanedione might, if successful, constitute a useful route to angular-substituted 4-ketotetrahydrocarbazoles of the type I. Furthermore, if the angular group were

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(5) R. Adams and W. P. Samuels, *J. Am. Chem. Soc.*, **77**, 5375, 5383 (1955).