Formation of Basic Compounds During the Indole Cyclization of Ketone Phenylhydrazones

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On the basis of previous occasional findings, the Fischer indole cyclization of ten ketone phenylhydrazones containing moieties of increasing bulkiness was investigated in order to isolate eventual side products. In the cases of the three 2-, 3- and 4-acetylpyridine phenylhydrazones the corresponding 2-pyridylindoles were the sole compounds so far isolated. In all the remaining cases, beside the indoles a mixture of basic compounds was obtained. In all cases aniline and a 2-substituted (2-methyl or 2-phenyl)benzimidazole were formed, the last resulting through an apparent *ortho*-semidinic rearrangements of phenylhydrazones. Starting from methyl isopropyl ketone phenylhydrazone a compound of formula $C_{11}H_{15}NO$ was also isolated, to which the structure of 3-(4-aminophenyl)-3-methylbutanone was assigned on the basis of ir, nmr spectra and of the chemical reactivity. The formation of this compound seems related to a *para*-benzidine-like rearrangement of phenyl hydrazone.

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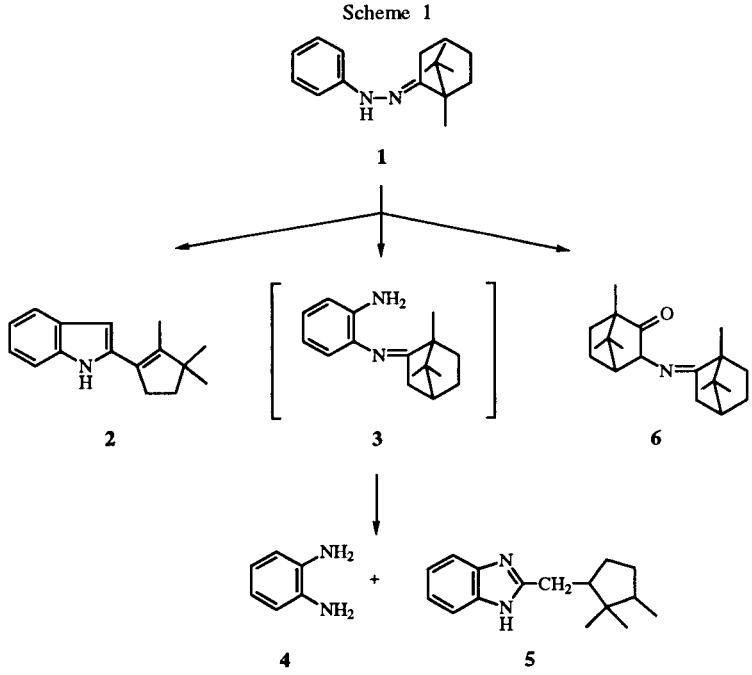
Introduction.

More than thirty years ago, during the reexamination of the cyclizaction of camphor phenylhydrazone (**1**), already studied by Kuroda [1], beside a small amount of the so called camphoindole (**2**) (whose structure was later demonstrated to be different from the one expected), one of us isolated a number of substances [2,3], among which were identified *ortho*-phenylenediamine (**4**), 2-(2,2,3-trimethylcyclopentyl)methylbenzimidazole (**5**) and 3-(camphoramino)camphor (**6**).

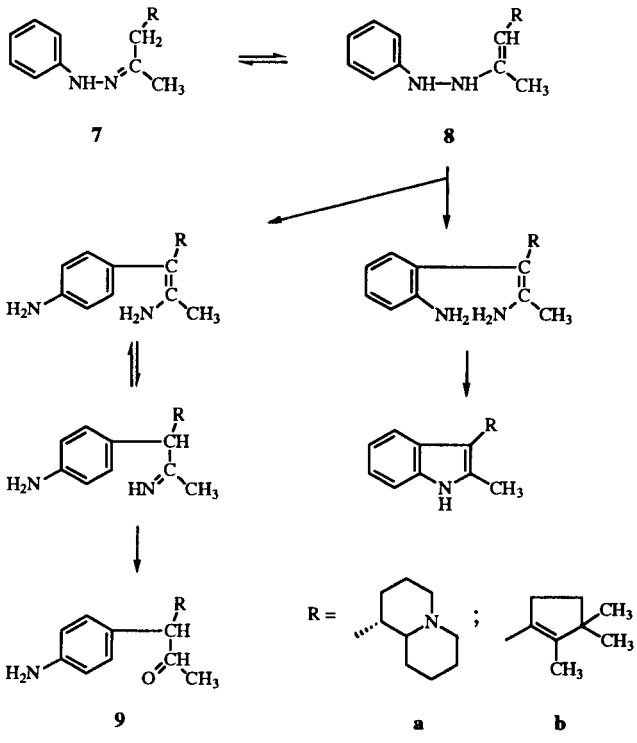
The formation of **4** and **5** was tentatively rationalized assuming as the intermediate, 2-(camphoramino)aniline (**3**), resulting from a *ortho*-semidine-like rearrangement of the phenylhydrazone.

On the other hand, a few years later, during the preparation of a set of 2-methyl-3-quinolizidinyl-5-*R*-indoles of pharmacological interest [4,5], we observed that the ethanolic hydrogen chloride cyclization of quinolizidinylacetone phenylhydrazone (**7a**) afforded as the main product, beside a small amount of the expected indole, the 1-(4-aminophenyl)-1-(quinolizidin-1'- yl)acetone (**9a**) [6,7]. Similarly, from the cyclization of β-methylcampholenone phenylhydrazone (**7b**), together with the expected indole, a basic compound $C_{17}H_{23}NO$ was obtained, to which the structure of 1-(4-aminophenyl)-1-(2,3,3-trimethylcyclopenten-1-yl) acetone (**9b**) was tentatively assigned. It was suggested that these peculiar compounds originated through *para*-benzidine-like rearrange-

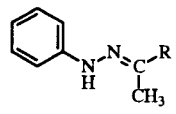
Scheme 1



Scheme 2



Scheme 3



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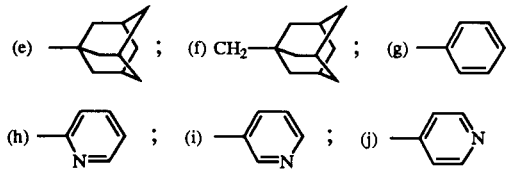
R = (a) CH_3; (b) CH_2–CH_3; (c) $CH(CH_3)_2$; (d) $C(CH_3)_3$



ments of enehydrazines **8a** and **8b**, along with *ortho*-benzidine type intermediates that provide indoles.

In spite of the huge number of arylhydrazones submitted to the cyclization, formation of compounds coming from *ortho*-semidine-like and *para*-benzidine-like rearrangements had never been reported.

Actually, the formation of *ortho*-phenylenediamine was already described by Theilacker and Leichtle [8], although starting from the benzophenone acetylphenylhydrazone not susceptible to indole cyclization.

In such a situation, from that time to the present we devoted painstaking efforts in order to isolate the eventual side product of the acid-induced cyclization of many arylhydrazones that were examined during our investigations on indole derivatives of pharmacological interest which were purposely selected to integrate the results obtained with the former research objectives.

Since the ketones used for the above described cyclization were characterized by the presence of bulky residues, it might be possible that the peculiar results were somehow linked to such a structural feature. In order to check this possibility we investigated the cyclization of ten ketone phenylhydrazones possessing moieties of increasing bulkiness. Partial results of this investigation have been reported [9,10]. The compounds examined are shown in Scheme 3.

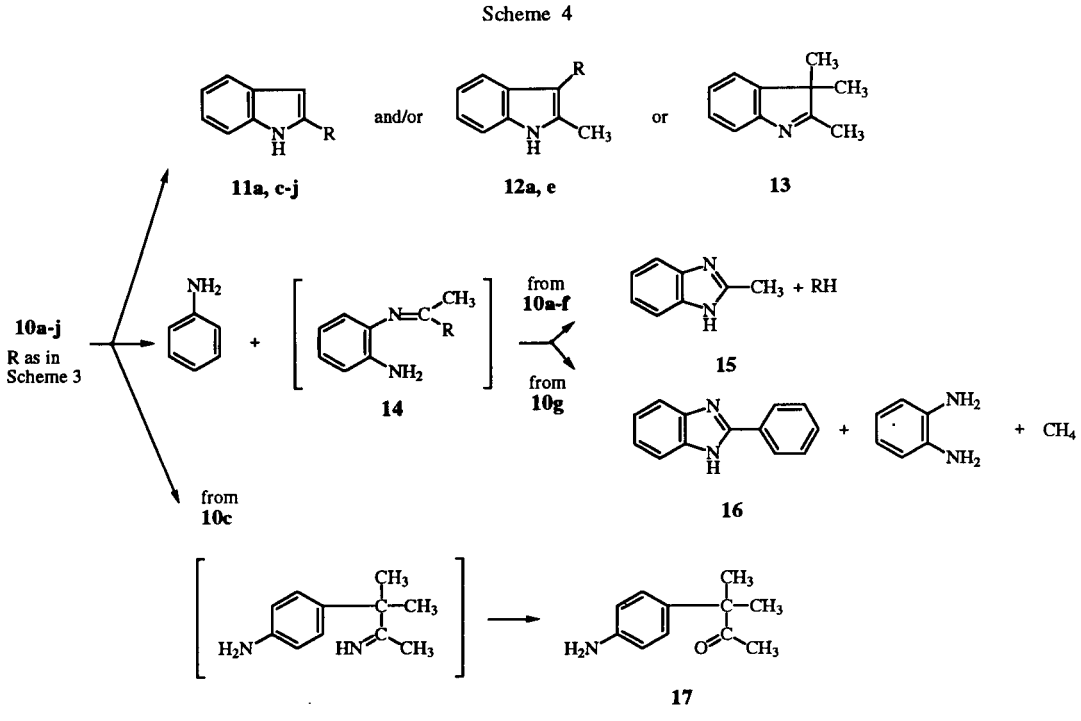
The cyclization of compounds **10a-10g** was performed by heating them with zinc chloride; in the case of adamantylacetone phenylhydrazone (**10f**), the only compound never studied by others, the cyclization by means of hydrogen chloride in propionic acid and of polyphosphoric acid were also attempted. For the phenylhydrazones of the three acetylpyridines **10h-10j** polyphosphoric acid was used.

In the cases of the three acetylpyridine phenylhydrazones **10h-10j,** the corresponding 2-pyridylindoles **11h-11j** were the sole compounds so far isolated, while in all the remaining cases we obtained other compounds in addition to the indoles.

With regard to the indoles, we observed that the zinc chloride-induced cyclization of the unsymmetrical ketone phenylhydrazones **10b, 10c, 10f** allowing the specific indolization reaction to take place in two different directions, gave different results depending on the substituents (Scheme 4). From **10b** only indole **12a** was isolated, while from **10c** the indolenine **13** was the main product, both corresponding to the involvement of the methylene or methine group adjacent to the carbonyl. In the last case, 2-isopropylindole (**11c**) was formed simultaneously. In the case of **10f** the cyclization involved preferentially the methyl group giving the 2-(1-adamantyl)methylindole (**11f**). The same results were accomplished using a large excess of polyphosphoric acid, while with hydrogen chloride in propionic acid, 2-methyl-3-(1-adamantyl)indole **12e** was formed.

Reaction of the methyl group instead of the methylene group, although rather unusual, had already been observed as the results of the use of a particular cyclization catalyst [11]. The formation of 2-isopropylindole prevailed over that of 2,3,3-trimethylindolenine when sulphuric acid was used, but it was never observed in a zinc chloride induced cyclization [12]. In the cyclization of phenylhydrazones **10a-10g,** a mixture of basic products was always formed. In *all* cases aniline and a 2-substituted benzimidazole (2-methyl from **10a-10f;** 2-phenyl from **10g**) were formed independently from the occurence of steric hindrance. Starting from methyl isopropyl ketone phenylhydrazone **10c** and acetophenone phenylhydrazone

Scheme 4



10g, respectively a compound $C_{11}H_{15}NO$ and *ortho*-phenylenediamine were isolated in addition.

The nmr spectrum of the compound of formula $C_{11}H_{15}NO$ exhibited a singlet at δ 1.41 (6H, $2CH_3$), a singlet at δ 1.9 (3H, CH_3-CO), a broad singlet at δ 3.5 (2H, NH_2) collapsing after exchange with deuterium oxide and two doublets centered at δ 6.61 and 7.11 (J ≅ 6 cps) corresponding to 4 protons in the *para*-disubstituted benzene ring. The presence of the methylcarbonyl group was confirmed by the ir spectrum (ν 1700 cm^{-1}) and the formation of iodoform (Lieben test). The amino group was susceptible to diazotization thus it was connected to the benzene ring. Therefore the structure of 3-(4-aminophenyl)-3-methylbutanone (**17**) was attributed to this compound which corresponds to the aminoketones **9a** and **9b** previously described as products of a *para*-benzidine-like rearrangement.

2-Methylbenzimidazole, consistently formed in the cyclization of methylketone phenylhydrazones, originates, quite probably, from the thermal decomposition of 2-(methylalkylideneamino)anilines resulting from an apparent *ortho*-semidine rearrangement of phenylhydrazones as already advanced for camphor phenylhydrazone.

In accordance with the observations of Elderfield *et al.* [13-15] the carbon-carbon bond which is broken by heating the Schiff bases is the one proceeding from the carbon atom having the greater degree of substitution. However, in contrast with this was the formation of 2-phenylbenzimidazole from acetophenone phenylhydrazone with loss of the methyl group. However exceptions to the above rule were already pointed out by Elderfield in that by heating methyl cyclopropyl ketone with *ortho*-phenylenediamine provided 2-cyclopropylbenzimidazole with evolution of methane.

Table I

Reaction Conditions and Yields of Neutral and Basic Fractions of Zinc Chloride Induced Cyclizations

Starting phenylhydrazone	Reaction conditions temperature °C (time, minutes)	Crude neutral fraction yield % [a]	Crude basic fraction yield % [a]	Crude basic fraction isolated compounds
10a	180 (1+5)	50	12	aniline + 15
10b	180 (1+5)	66	4.5	aniline + 15
10c	100 (4+30)	8	73	aniline + 13 [b] + 15 + 17
10d	105 (10), 130 (30), 190 (4)	75	9.0	aniline + 15
	190 (4 + 5)	65	18	
10e	185 (10)	88	5.6	aniline + 15
10f	105 (5), 190 (2 + 2)	86	7.0	aniline + 15
10g	170 (12)	91	3.0	aniline + *o*-phenylenediamine + 16

[a] Yields are given as percentage of the weight of the starting material. [b] Yield 67%.

The isolation of *ortho*-phenylenediamine among the cyclization products strongly supports the intermediate formation of a Schiff base through cleavage of the N-N-bond and subsequent connection of the imine moiety at the position *ortho* to the other nitrogen atom.

The formation of *ortho*-phenylenediamine derivatives was also postulated by Fusco *et. al.* [16] that by heating with polyphosphoric acid the arylhydrazones of phenylglyoxylic esters, 3-phenyl-1-methylquinoxalin-2(1*H*)-ones were the products. These authors demonstrated that such an *ortho*-semidine-like rearrangement was unequivocally intramolecular.

Therefore on this basis our earlier suggestion [3,17] of a N-N bond homolytic cleavage as a key step for the formation of all compounds in Scheme 1 should be discarded, although this would leave unexplained the formation of compound **6**.

Actually it may be possible that more than one mechanism is operating under the reaction conditions, or that the reaction path could vary with the nature of a single substrate.

It is worth noting that, considering the cyclizations formerly and presently studied, the *ortho*-semidine-like rearrangement seems to be of rather general significance, while the *para*-benzidine-like reaction occurred only in a few cases. Thus additional investigations are warranted to define which, if any, structural feature is responsible, respectively, for the two types of rearrangement.

EXPERIMENTAL

Melting points were determined by the capillary method on a Büchi apparatus and are uncorrected. The elemental analyses were performed at the Microanalytical Laboratory of the "Dipartimento di Scienze Farmaceutiche" of Genoa University. The uv and ir spectra were recorded, respectively, with a Varian DMS 80 and Perkin Elmer mod. 197 spectrophotometer; ^{1}H-nmr spectra were taken on a Hitachi-Perkin Elmer R-600 spectrometer using deuteriochloroform with tetramethylsilane as the internal standard.

Ketones.

All required ketones were commercially available with the exceptions of 1-acetyladamantane and 1-adamantylacetone that were prepared according to the references [18] and [19] respectively.

Phenylhydrazones.

Equimolar amounts of ketone and phenylhydrazine were heated for 2 hours at 100° under a stream of dry nitrogen; the formed water was then removed under reduced pressure (20 Torr). The obtained phenylhydrazones **10e-j** were used immediately as such, while the phenylhydrazones **10a-d** were distilled at 0.1 Torr.

Cyclization with Zinc Chloride of Phenylhydrazones **10a-g**.

The freshly prepared phenylhydrazones (10-15 g) were mixed with twice their weight of dry zinc chloride, finely ground in a dry-box. The flask containing the mixture was immersed under a stream of dry nitrogen in a oil bath generally preheated at 170-190°. In most cases a violent reaction occurred and the flask was withdrawn from the bath for a while and then heated again for the total time indicated in Table I. After cooling, the mixture was taken up with aqueous 1*M* hydrochloric acid (150-175 ml). The acid solution was filtered and extracted several times with ether to obtain a *neutral fraction* containing the indole.

In the case of acetophenone phenylhydrazone (**10g**) cyclization, the melted mixture was mixed with sand, allowed to cool and then triturated with acid. The insoluble material was air dried and then extracted with boiling ethanol.

In all cases the acid solution was basified with strong ammonia and thoroughly extracted with ether in order to collect all the basic *compounds* eventually formed.

Work Up of the Neutral Fractions. Indoles **11a, c-g, 12a.**

The ether (or ethanol) solutions of the neutral fractions were evaporated to dryness and the residues crystallized from different solvents as indicated for each compound.

2-Methylindole **11a**.

This compound was obtained as leaflets (aqueous ethanol), mp 56-57°, lit [20] 59°.

2,3-Dimethylindole **12a**.

This compound was obtained as leaflets (hexane), mp 104-105° (hexane), lit [21] 106°.

2-Isopropylindole **11c.**

This compound was obtained as prismatic crystals (dry ether-pentane), mp 73-74° according to the literature method [12]; uv (ethanol): λmax 272.5, 277 sh, 288 nm.

2-*tert*-Butylindole **11d.**

This compound was obtained as prismatic crystals (dry ether-pentane), mp 72-73° according to the literature method [22]; uv (ethanol): λmax 273, 278, 282, 290 nm.

2-(1-Adamantyl)indole **11e**.

The crude neutral fraction was extracted several times with boiling pentane leaving some dark red material. The pentane extract was evaporated and the residue was crystallized from dry ether-pentane, mp 148-150° according to the literature method [23]; uv (ethanol): λmax 221, 280, 288 nm; ^{1}H nmr: δ 7.9-7.2 (m, 5H, benzene protons + NH), 6.25 (d, 1H, indole 3-H), 1.9-1.72 (m, 15H, adamantyl residue).

2-[(1-Adamantyl)methyl]indole **11f**.

The crude neutral residue was extracted several times with boiling pentane leaving some dark red material. The pentane extract was evaporated and the residue was chromatographed on silica gel (ratio 1:40) eluting with a mixture of hexane-dry ether (2:1). Compound **11f** was obtained as prismatic crystals (dry ether), mp 147-148°; uv (ethanol): λmax 219, 274 sh, 278, 287 nm; ^{1}H nmr: δ 7.8-6.9 (m, 5H, benzene protons + NH), 6.25 (s, 1H, indole 3-H), 2.4 (s, 2H, CH_2), 2.05-1.3 (m, 15H, adamantyl residue).

Anal. Calcd. for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.99; H, 8.86; N, 5.51.

2-Phenylindole **11g**.

This compound was obtained as leaflets (ethanol), mp 188-189° according to the literature method [24].

Working Up of the Basic Fractions.

The ether solutions of the basic fractions were evaporated to dryness and the residue was worked up differently depending on the state (oily or solid) and based upon their preliminary tlc examination.

a) The solid basic fraction resulting from pinacolone phenylhydrazone (**10d**) was rinsed with dry ether leaving crystals melting at 174-176° (2-methylbenzimidazole: see below).

From the ethereal washings some aniline was recovered and identified by formation of the acetyl derivative (mp and mixed mp with acetanilide 110-112°).

b) The basic fractions obtained from phenylhydrazones **10a-c, e, f** were distilled under reduced pressure (20 Torr) heating to about 100° (air bath temperature) to remove the aniline that was characterized as the acetyl derivative as above.

In the case of **10c**, raising the air bath temperature to 105-110° a second, very abundant, fraction was obtained that was identified as 2,3,3-trimethylindolenine (see below).

The distillation residues were either treated with dry ether **10e** and **10f** to obtain a crystalline product with mp 167-171° (2-methylbenzimidazole), or further distilled under vacuum (0.1-0.2 Torr) heating to 160°. The very viscous oil that was obtained sometimes mixed with crystals, and the final distillation residue was chromatographed on neutral alumina using dichloromethane as the eluent, followed by dichloromethane plus 1% methanol.

Sometimes the dichloromethane eluted fractions exhibited the presence of a carbonyl group (band at 1700 cm^{-1} in the ir spectra) and/or of a primary aromatic amino group (diazotization test), suggesting the existence of the purported *para*-benzidine and/or *ortho*-semidine-like rearrangement products, though only in the case of phenylhydrazone **10c** was it possible to isolate, after a second chromatography, a pure compound melting at 81-83° (**17**) (see below). The fractions eluted with dichloromethane plus methanol when treated with a little of dry ether yielded crystals melting at 174-176°, 2-methylbenzimidazole.

c) The basic fraction resulting from acetophenone phenylhydrazone (**10g**) was distilled directly at 0.1-0.2 Torr, collecting under 60° (air bath temperature) an oil (identified as usual as aniline) and thereafter a solid compound in typical square plates which after washing with hexane melted at 103° (*o*-phenylenediamine, see below). The distillation residue was washed several times with dry ether leaving some tiny, greenish needles melting at 290-293° (2-phenylbenzimidazole, see below).

Identification of the Basic Compounds: *o*-Phenylenediamine.

The compound crystallized as square plates obtained from phenylhydrazone **10g** gave a purple precipitate when treated with ferric chloride solution; mp 103°; mixed mp with authentic *o*-phenylenediamine was undepressed.

2-Methylbenzimidazole (**15**).

The needles melting either at 167-171° or at 174-176° (which were obtained from phenylhydrazones **10a-f**) after repeated crystallization from water had mp 174.5-176.5°. The uv spectra in ethanol (λmax 243, 274, 280 nm) and in 1*N* hydrochloric acid (λmax 236, 268, 275 nm) were superimposable with those of 2-methylbenzimidazole [25]. Mixed mp with commercial 2-methylbenzimidazole was unchanged.

2-Phenylbenzimidazole (**16**).

The greenish needles melting at 290-293° obtained from **10g** gave uv spectrum in ethanol (λmax 218sh, 241, 247sh, 297sh, 304, 316 nm) conforming to the literature [25]. Mixed mp with commercial 2-phenylbenzimidazole melting at 293-296° was undepressed.

2,3,3-Trimethylindolenine (**13**).

The oily basic fraction (bp 100-105°) obtained from phenylhydrazone **10c** gave a picrate (ethanol) melting at 157-158°, according to the literature method [26] ; ^1H nmr: δ 7.6-7.1 (m, 4H, benzene ring; 2.29 (s, 3H, CH_3 in position 2); 1.3 (s, 6H, $2CH_3$ in position 3).

3-(4-Aminophenyl)-3-methylbutanone (**17**).

This compound was isolated from the basic fraction obtained from **10c** through a repeated chromatography of the fraction distilled between 110° and 160° (0.1-0.2 Torr); mp 81-83° (dry ether-pentane). The ir spectrum (chloroform) showed a carbonyl band at 1700 cm^{-1}; the positive iodoform test indicated the presence, of a methyl group near to the carbonyl. The positive diazotization supported the presence of a primary amino group on the benzene ring; ^1H nmr: δ 7.11 and 6.61 (dd; J = 6 cps; 4H in *para*-disubstituted benzene); 2.5 (broad s; 2H, NH_2; disappears after deuterium oxide exchange); 1.90 (s, 3H, CH_3-CO); 1.41 (s, 6H, $C(CH_3)_2$).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74,80; H, 8.27; N, 7.85.

Attempt of Cyclization of Pinacolone Phenylhydrazone (**10d**) with Ethanolic Hydrogen Chloride.

The phenylhydrazone (14 g) was dissolved in absolute ethanol (140 ml) and the ice-cooled solution was saturated with dry hydrogen chloride. The solution was boiled under reflux and resaturated with dry hydrogen chloride every 3 hours; the heating was continued for a total of 30 hours. After cooling the precipitate was collected, washed with dry ether and identified as phenylhydrazine hydrochloride; mp and mixed mp (vacuum sealed capillary) 240-250° with decomposition.

Neither 2-*tert*-butylindole, nor 2-methylbenzimidazole could be detected in the filtrate solution.

Cyclization of 1-Adamantylacetone Phenylhydrazone **10f** with Propionic Acid and Hydrogen Chloride.

The phenylhydrazone **10f** (2.8 g) was dissolved in 30 ml of propionic acid and the ice-cooled solution was saturated with dry hydrogen chloride and then refluxed for 1 hour under a stream of nitrogen. The solvent was removed under reduced pressure and the neutral and basic compounds were separated as usual. The basic fraction (~ 50 mg) was represented by aniline only, recognized as acetanilide.

The neutral fraction (2.58 g) was distilled at 0.1 Torr giving a first (0.3 g) fraction (air bath temp. <110°) that with dry ether-pentane yielded crystals melting at 107° either alone or mixed with *N*-propionylaniline, and a second fraction (air bath temp. 110-140°) that after chromatography on silica gel (dichloromethane as eluent) gave crystals melting at 139-141° of 3-(1-adamantyl)-2-methylindole (**12e**).

3-(1-Adamantyl)-2-methylindole **12e**.

This compound was obtained as prismatic crystals (pentane), mp 139-142°; uv. spectrum (ethanol): λmax 225, 276sh, 282, 288 nm; ^1H nmr: δ 8.1-6.9 (m, 5H; benzene protons + NH); 2.42 (s, 3H; 2-CH_3); 2.3-1.7 (m, 15H; adamantyl residue).

Anal. Calcd. for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.64 ; H, 8.71 ; N, 5.44.

Cyclization of 1-Adamantylacetone Phenylhydrazone **10f** with Polyphosphoric Acid.

A mixture of phenylhydrazone **10f** (2.2 g) and polyphosphoric acid (33.5 g) was heated at 135° for 20 minutes under a stream of nitrogen.

After cooling the mixture was taken up with water and filtered. The solid obtained (1.85 g, 89.5% yield) was treated several times with a hot mixture of dry ether and pentane. The extracts were evaporated and the residue was chromatographed on a column of silica gel (ratio 1:40). Elution with pentane-dry ether (1:1) gave crystals melting at 147-148° of 2-[(1-adamantyl)methyl]indole (**11f**).

The basic fraction was negligible.

Cyclization of 2-, 3- and 4-Acetylpyridine Phenylhydrazones (**10h-j**) with polyphosphoric acid.

A mixture of phenylhydrazone (8.7 g) and polyphosphoric acid (27 g) was rapidly heated up to 180° in an oil bath under a stream of nitrogen and maintained at this temperature for 5 minutes, following the indications of [27]. After cooling the mixture was taken up with water, basified with aqueous 6*N* sodium hydroxide solution and thoroughly extracted with ether. After removing the solvent, the residue was rinsed with dry ether obtaining the corresponding 2-(2-, 3-, 4-pyridyl)indoles that were crystallized from benzene; yields were in the range 83-61%. Crystals obtained melted at 151-153° (**11h**), 169-170° (**11i**), 196-198° (**11j**), in good agreement with the literature data [27], as it was for ethanolic uv absorption maxima which were, respectively, 325 nm (**11h**), 315 nm (**11i**), 330 nm (**11j**). The ethereal washings and the crystallization mothers were evaporated to dryness and the residues were chromatographed on silica gel eluting with ether and then with ether plus 1% diethylamine, or on alumina eluting with ether followed by ether plus 1% methanol. In any cases, no evidence was achieved for the presence of other basic compounds apart from the expected pyridylindoles.

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