The Synthesis of Indazoles *via* 2,3-Dihydroindazoles (1)

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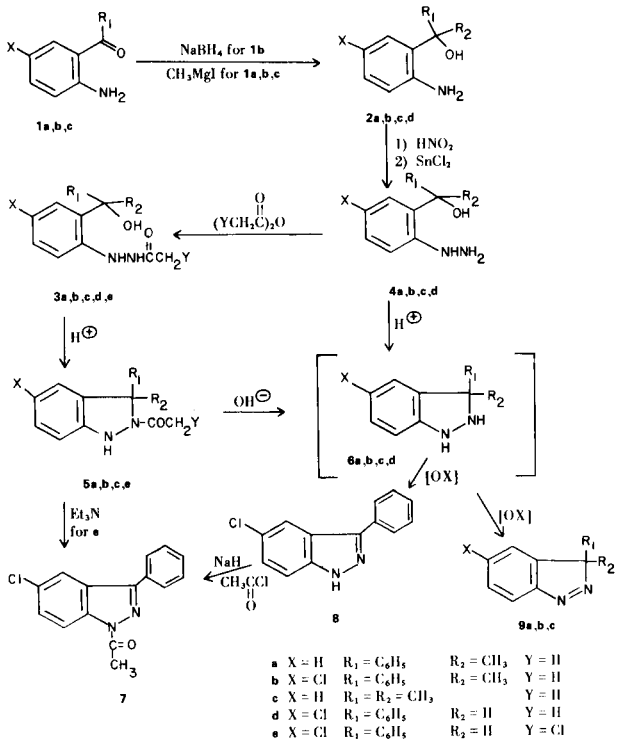
The preparation and oxidation of 2,3-dihydroindazoles to 1*H*,2*H* or 3*H*-indazoles is described. A method for the synthesis of indazole 2-oxides has been found. Oxidation of 2-acetyl-2,3-dihydro-3,3-disubstituted indazoles **5a** and **5c** gave quinoid compounds **20a**, **20b**, **24a** and **24b**, which could be isomerized to 3*H*-indazoles upon removal of the acetyl group. A quinoid compound **21** was also obtained on treatment of **5a** with tetracyanoethylene.

2-Acylanilines, in particular 2-aminobenzophenones, have been used as starting materials in the synthesis of a variety of heterocyclic compounds such as indoles, quinazolines and benzodiazepines (2). We would now like to report on the utility of these compounds as intermediates for the synthesis of 2,3-dihydroindazoles and indazoles. The preparation of indazoles from 2-acylanilines **1** (Scheme I) by diazotization and reduction is well known and has been applied to 2-amino-5-chlorobenzophenone. The preparation and chemistry of 2,3-dihydroindazoles has been largely unexplored (3) and therefore attracted our attention.

The carbinols **2** were prepared either by reduction of the ketones **1** with sodium borohydride or by reaction of the ketones with methylmagnesium iodide according to literature procedures. The carbinols **2** were diazotized in hydrochloric acid and the resulting diazonium salts were reduced with stannous chloride to afford the corresponding hydrazines **4** in moderate yields. Acylation in two-phase systems yielded the monoacyl derivatives **3** which were cyclized to the corresponding 2-acyl-2,3-dihydroindazoles **5** by treatment with strong acid, presumable by initial carbonium ion formation followed by ring closure.

Hydrolysis of the acyl group led to the 2,3-dihydroindazoles **6**. These compounds were also formed by direct acid catalyzed cyclization of the hydrazines **4**. While the acyl derivatives **5** are relatively stable compounds, the dihydroindazoles **6** proved to be air sensitive and, in general, they were not isolated but were oxidized *in situ* to afford the corresponding 1*H* or 3*H*-indazoles **8** or **9**, depending on the substituents in the 3-position. Treatment of **6a**, **b** and **c** with manganese dioxide in methylene chloride gave the corresponding indazoles **9a**, **b** and **c**. In the case of **6d**, oxidation to the indazole **8** occurred in the reaction mixture. Compound **6b** was isolated as its sulfuric acid addition salt in 70% yield by diluting the reaction mixture with a measured amount of ice water.

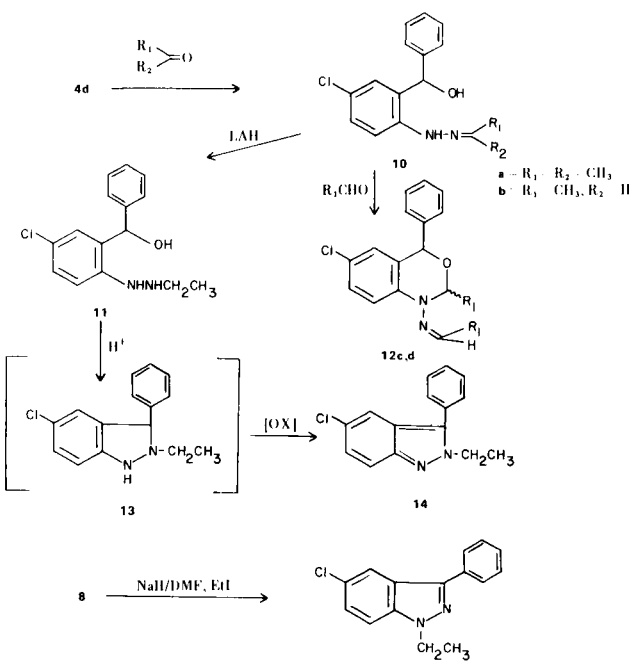
Scheme I



In the special case of the chloroacetate **5e**, treatment with triethylamine gave 1-acetyl-3-phenyl-5-chloroindazole **7** in low yield. One explanation for this interesting transformation would be an initial proton abstraction by the triethylamine, followed by the splitting out of ketene, and subsequent reaction of the ketene with the indazole thus formed.

The reaction of the hydrazine **4d** with carbonyl compounds was also examined (Scheme II). Condensation of the hydrazine **4d** with acetone led to the hydrazone **10a**. The reaction of **4d** with acetaldehyde was more

Scheme II



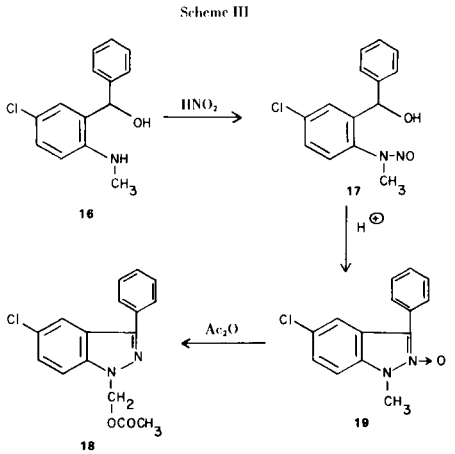
complex. Thus at room temperature in methylene chloride solution, the Schiff base **10b** formed which was smoothly reduced with lithium aluminum hydride to **11**. Ring closure of **11** with concentrated sulfuric acid gave the intermediate **13** which proved to be very susceptible to oxidation and 5-chloro-2-ethyl-3-phenyl-2*H*-indazole **14** was obtained directly from the reaction mixture. This synthetic pathway is an unambiguous method for the preparation of 2-alkylindazoles, although in some cases it has been reported that such compounds can be obtained directly from indazole by alkylation, depending on the conditions used. The isomeric 1-alkylindazole **15** was prepared for comparative purposes by using standard alkylation procedures. It was observed that under more vigorous conditions the reaction of compound **4d** with acetaldehyde did not stop at the Schiff base but went on to yield the two isomeric oxazines **12c** and **12d**, of undetermined stereochemistry. The nmr spectra suggest that these compounds are *syn* and *anti* isomers because rapid interconversion was noticed under acid catalysis (trifluoroacetic acid in deuteriochloroform).

An interesting route leading to the formation of indazole 2-oxides is shown in Scheme III. The reaction of the *N*-methylaniline **16** with nitrous acid gave the corresponding nitroso compound **17** which on treatment with concentrated sulfuric acid yielded the indazole 2-oxide **19**. The nitrone underwent a Polonovsky type rearrangement using acetic anhydride under vigorous conditions to afford 1-acetoxymethyl-5-chloro-3-phenyl-1*H*-indazole, compound **18**.

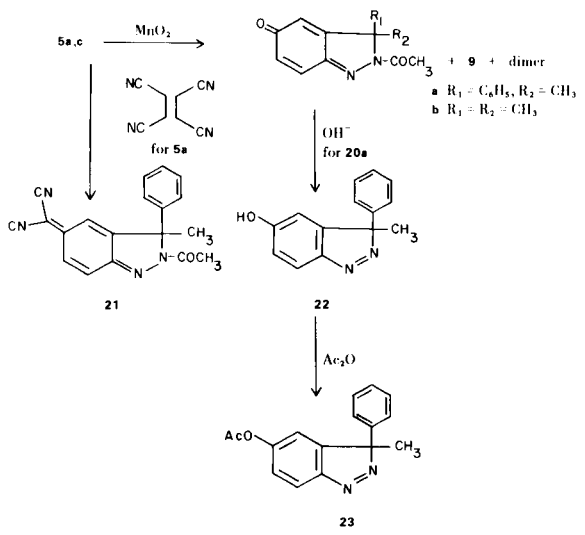
It was observed that the deschloro-2-acetyl-dihydroindazoles **5a** and **5c** took on a purple cast on prolonged standing in air. When these compounds in methylene chloride solution were oxidized by manganese dioxide, the quinoidal compounds **20a** and **20b**, together with the 3,3-disubstituted indazoles **9a** and **9c** and small amounts of deeply colored dimeric materials were isolated (Scheme IV). The structure of the quinoidal compounds was evident from the spectral data, expecially the nmr spectra. H_7 has the highest chemical shift, showing a coupling constant of 10 Hz with H_6. H_6 is further coupled with H_4 with a coupling constant of 2 Hz. In order to further rule out the possibility of an *o*-quinone structure, the oxidation of the *p*-chloro analog **5b** was attempted. However, as expected, no quinoidal product was obtained. When compound **20a** was treated with aqueous sodium hydroxide, the acetyl group was lost and the compound isomerized to yield the 5-hydroxyindazole **22**. Treatment of **22** with acetic anhydride afforded the acetoxy derivative **23**.

It was found that the 2-acetyl-2,3-dihydroindazoles reacted with tetracyanoethylene in a manner similar to that of isobenzimidazoles reported by Herbert and coworkers (4). Thus compound **5a**, when treated with tetracyanoethylene, afforded the dicyanomethylene derivative **21**. The formation of this compound is best explained by electrophilic addition of tetracyanoethylene to **5a** followed by a proton shift and elimination of malononitrile. An attempt to prepare a derivative analogous to **21** by an oxidative coupling reaction with diethyl malonate using manganese dioxide as oxidizing agent afforded a mixture of the isomeric dimeric quinoidal compounds **24a** and **24b** (Scheme V). Spectra indicated that the product was a mixture of isomers, although the deep purple solid appears to be crystalline and melts fairly sharply. Hydrolysis of the mixture with aqueous sodium hydroxide, followed by oxidation of the intermediate **26** with manganese dioxide, gave the dimeric indazole **25**. This compound exists in two stereoisomeric forms, one of which was isolated in

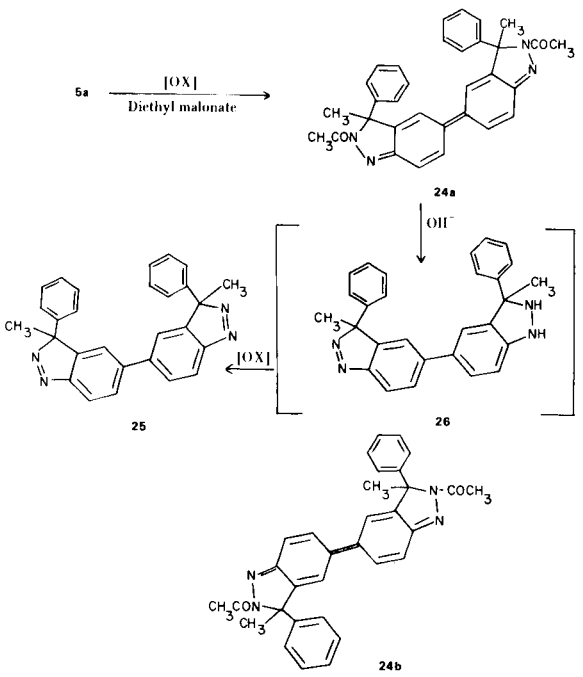
Scheme III



Scheme IV



Scheme V



pure form by fractional recrystallization. While the absolute stereochemistry has not been determined, the nmr spectrum, with a sharp singlet for the two methyl groups would indicate that the molecule is symmetrical.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument in deuteriochloroform with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. The mass spectra were determined on a CEC-21-110 B instrument at 70 eV. Silica gel Merck (70-230 mesh) was used for chromatography.

2-(α-Hydroxy-α-methylbenzyl)phenylhydrazine (**4a**).

2-(α-Hydroxy-α-methylbenzyl)aniline (**2a**) (5) (41.2 g., 0.19 mole) was added to 200 ml. of 6*N* hydrochloric acid and the mixture was cooled with stirring to -3°. Sodium nitrite (14.0 g., 0.2 mole) dissolved in 50 ml. of water was added dropwise over 3 minutes and the reaction mixture stirred for 2 minutes longer when cooling was discontinued. Stannous chloride dihydrate (90.0 g., 0.4 mole) was added. When the temperature reached 19°, the mixture was cooled to 5°, and maintained there for 20 minutes, diluted with 500 ml. of water, made alkaline by the addition of aqueous sodium hydroxide and extracted with methylene chloride. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The oily residue crystallized from a mixture of ether-petroleum ether (30-60°) to yield 21.0 g. (49%) of product, m.p. 98-101°; ir (chloroform): 3400 cm^{-1} (OH); uv: λ max 206 mμ (ε, 37,250), 245 (8,700), 292 (2,450).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.9; H, 7.0; N, 12.3.

4-Chloro-2-(α-hydroxy-α-methylbenzyl)phenylhydrazine (**4b**).

2-Amino-5-chloro-α-methylbenzhydrol (**2b**) (6) (24.7 g., 0.10 mole) was added to 300 ml. of 6*N* hydrochloric acid and cooled with stirring to 5°. Sodium nitrite (7.5 g., 0.11 mole) dissolved in 25 ml. of water was added dropwise, followed by 500 g. (0.22 mole) of stannous chloride dihydrate. The mixture was stirred at 0° for 1 hour and the solid collected and partitioned between methylene chloride and aqueous ammonia. The methylene chloride layer was dried and evaporated. The product was recrystallized from methylene chloride-petroleum ether to yield 10.0 g. (38%) of colorless prisms; m.p. 139-141°; ir (chloroform): 3380 cm^{-1} (OH); uv: λ max 253 mμ (ε, 13,200), 305 (2,500).

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.0; H, 5.7; N, 10.7. Found: C, 64.1; H, 5.9; N, 10.7.

2-Hydrazinophenyldimethylcarbinol (**4c**).

2-Aminophenyldimethylcarbinol (**2c**) (7) (41.0 g., 0.28 mole) was dissolved in 270 ml. of 6*N* hydrochloric acid and cooled with stirring to -20°. Sodium nitrite (19.0 g., 0.27 mole) dissolved in 55 ml. of water was added while maintaining the temperature at -15°. Stannous chloride dihydrate (120 g., 0.53 mole) was added in portions, and the reaction mixture stirred at -15° for 30 minutes, 5° for an additional 30 minutes and then partitioned between aqueous ammonia and methylene chloride. The organic phase was dried and evaporated. Crystallization of the residue from ether-petroleum ether yielded 16.4 g. (35%) of product melting at 112-114°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 115-118°; ir (chloroform): 3400 cm^{-1} (OH); uv: λ max 244 mμ (ε, 9,800), 290-292 (2,400).

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.0; H, 8.5; N, 16.8. Found: C, 65.3; H, 8.7; N, 17.0.

4-Chloro-2-(α-hydroxybenzyl)phenylhydrazine (**4d**).

4-Chloro-2-(α-hydroxybenzyl)aniline (**2d**) (8) (31.5 g., 0.135 mole) was added to 150 ml. of 6*N* hydrochloric acid. The thick suspension was cooled with stirring to 5° and sodium nitrite (10.5 g., 0.152 mole) dissolved in 30 ml. of water was added dropwise, followed by 67.5 g. (0.30 mole) of stannous chloride dihydrate, added in portions over a period of 30 minutes. After 1 hour at 5°,

the gummy product was collected and partitioned between aqueous ammonia and ether. The ether layer was washed with sodium chloride solution, dried and evaporated. Crystallization of the residue from ether-petroleum ether yielded 14.9 g. (44%) of colorless prisms, m.p. 113-118°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 177.5-119°; ir (chloroform): 3375 cm^{-1} (OH); uv: λ max 252 mμ (ε, 11,100), 302, (2,500).

Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.8; H, 5.3; N, 11.3. Found: C, 62.6; H, 5.3; N, 11.3.

N-[2-(α-Hydroxy-α-methylbenzyl)anilino]acetamide (**3a**).

Two hundred ml. of a 10% sodium carbonate solution was added to a solution of 21.0 g. (0.092 mole) of 2-(α-hydroxy-α-methylbenzyl)phenylhydrazine (**4a**) and 12.0 g. (0.12 mole) of acetic anhydride in 200 ml. of methylene chloride. The two phase reaction mixture was stirred at room temperature for 1 hour, enough methylene chloride added to dissolve the precipitated product and the layers separated. The organic phase was dried and evaporated. The residue was triturated with petroleum ether to yield 21.5 g. (87%) of product, m.p. 165-166°; ir (potassium bromide): 1650 cm^{-1} (C=O); uv: λ max 239 mμ (ε, 10,100), 288 (2,530).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.0; H, 6.6; N, 10.5.

N-[2-(α-Hydroxy-α-methylbenzyl)-4-chloroanilino]acetamide (**3b**).

This compound was obtained similarly in 87% yield from 11.1 g. (0.042 mole) of 2-(α-hydroxy-α-methylbenzyl)-4-chlorophenylhydrazine (**4b**) and 8.0 g. (0.09 mole) of acetic anhydride in 150 ml. of methylene chloride and 150 ml. of 10% sodium carbonate solution. The product melted at 153-154° dec. Recrystallization from methylene chloride-petroleum ether gave a crystal modification, m.p. 175-177° dec.; ir (chloroform): 1690 cm^{-1}; uv: λ max 248 mμ (ε, 13,950), 297-298 (2,580).

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C' 63.1; H, 5.6; N, 9.2. Found: C, 63.3; H, 5.6; N, 9.0.

2-(2-Acetylhydrazino)phenyldimethylcarbinol (**3c**).

Similarly, 14.2 g. (0.085 mole) of 2-hydrazinophenyldimethylcarbinol (**4c**) and 12.0 g. (0.12 mole) of acetic anhydride in 200 ml. of methylene chloride and 200 ml. of 10% sodium carbonate solution yielded 14.0 g. (79%) of colorless crystals, m.p. 137-139° after recrystallization from a mixture of methylene chloride and petroleum ether; ir (chloroform): 1690 cm^{-1} (C=O); uv: λ max 237-238 mμ (ε, 10,600), 283-286 (2,200).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.4; H, 7.7; N, 13.4. Found: C, 63.3; H, 7.8; N, 13.5.

N-(2-α-Hydroxylbenzyl-4-chloroanilino)acetamide (**3d**).

Acetyl chloride (4.7 g., 0.06 mole) was added slowly to a vigorously stirred two-phase mixture of 12.4 g. (0.05 mole) of 2-(α-hydroxybenzyl)-4-chlorophenylhydrazine (**4d**), 150 ml. of methylene chloride and 300 ml. of saturated sodium bicarbonate solution. After complete addition, stirring was continued until gas no longer evolved.

The reaction mixture was diluted with ether and filtered. The product was recrystallized from a mixture of methylene chloride, methanol and ether to yield 7.75 g. (54%) of **3d**, m.p. 183-186° dec; ir (potassium bromide): 1660 cm^{-1} (C=O); uv: λ max 248 mμ (ε, 12,047), 297 (2,269).

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 62.0; H, 5.2; N, 9.6; Cl, 12.2. Found: C, 61.7; H, 5.2; N, 9.5; Cl, 12.1.

N-([(2-α-Hydroxybenzyl)-4-chloro]anilino)chloroacetamide (**3e**).

Similarly, 10.0 g. (0.04 mole) of 2-(α-hydroxybenzyl)-4-chlorophenylhydrazine (**4d**), 5.6 g. (0.05 mole) of chloroacetyl chloride, 100 ml. of methylene chloride and 200 ml. of a saturated sodium bicarbonate solution yielded 8.6 g. (66%) of product, m.p. 150-151° dec., after recrystallization from a mixture of chloroform, methanol and petroleum ether; ir (potassium bromide): 1670 cm^{-1} (C=O); uv: λ max 245 mμ (ε, 4,450), 295 (1,000).

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_2$: C, 55.4; H, 4.3; N, 8.6. Found: C, 54.8; H, 4.2; N, 8.8.

2-Acetyl-2,3-dihydro-3-methyl-3-phenyl-1*H*-indazole (**5a**).

N-[2-(α-Hydroxy-α-methylbenzyl)anilino]acetamide (**3a**) (6.8 g., 0.025 mole) was treated with 20 ml. of trifluoroacetic acid. After the exothermic reaction subsided, the solution was allowed to stand at room temperature for 40 minutes, concentrated *in vacuo* to one-half its volume and the residual solution partitioned between methylene chloride and saturated sodium bicarbonate solution. The methylene chloride layer was dried and evaporated, and the residue crystallized from a mixture of ether and petroleum ether to yield 5.3 g. (84%) of a solid with a purple cast, m.p. 155-157° dec. The analytical sample was recrystallized from methylene chloride-petroleum ether to yield off-white prisms, m.p. 159-162° dec.; ir (chloroform): 1630 cm^{-1} (C=O); uv: λ max 247-248 mμ (ε, 9,200), infl 290 (2,250).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.2; H, 6.4; N, 11.1. Found: C, 76.5; H, 6.3; N, 11.0.

2-Acetyl-2,3-dihydro-3-methyl-3-phenyl-5-chloro-1*H*-indazole (**5b**).

N-[2-(α-Hydroxy-α-methylbenzyl)-4-chloroanilino]acetamide (**3b**) (1.0 g., 0.0033 mole) was treated with 2 ml. of concentrated sulfuric acid. The solution which formed was diluted with 30 ml. of ice-water and the precipitated product collected, washed with water and recrystallized from a mixture of methylene chloride-petroleum ether to yield 0.5 g. (53%) of off-white prisms, m.p. 151-154° dec. The analytical sample was recrystallized from the same mixture, m.p. 157-159° dec.; ir (chloroform): 1630 cm^{-1} (C=O); uv: λ max 257 mμ (ε, 11,400), sh 300 (2,020).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.0; H, 5.3; N, 9.8. Found: C, 66.9; H, 5.3; N, 9.8.

2-Acetyl-3-dimethyl-2,3-dihydro-1*H*-indazole (**5c**).

A solution of 11.2 g. (0.054 mole) of 2-(2-acetylhydrazino)-phenyldimethylcarbinol (**3c**) in 25 ml. of trifluoroacetic acid was allowed to stand at room temperature for 20 minutes and then partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried and evaporated. Trituration of the residue with petroleum ether gave 8.4 g. (82%) of a plum-colored solid, m.p. 157-164° dec. Recrystallization from methylene chloride-petroleum ether gave colorless crystals, m.p. 160-164.5° dec.; ir (chloroform): 1641 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.4; H, 7.4; N, 14.7. Found: C, 69.4; H, 7.6; N, 14.8.

2-Chloroacetyl-2,3-dihydro-3-phenyl-5-chloro-1*H*-indazole (**5e**).

N-([2-(α-Hydroxybenzyl)-4-chloro]anilino)chloroacetamide (**3e**) (7.0 g., 0.021 mole) was dissolved in 20 ml. of concentrated sulfuric acid. After standing for 3 minutes the solution was poured onto ice and the product collected, washed with water and recrystallized from a mixture of methylene chloride and petroleum ether to yield 5.3 g. (82%) of white needles, m.p. 153-155° dec. The analytical sample was recrystallized from the same mixture, m.p. 156-158° dec.; ir (chloroform): 1678 cm^{-1} (C=O); uv: λ max 247-248 mμ (ε, 9,850), sh 293-295 (2,300).

Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O$: C, 58.6; H, 3.9; N, 9.1.

Found: C, 58.6; H, 3.9; N, 9.2.

5-Chloro-3-phenylindazole (**8**) (9).

A mixture of 0.5 g. (0.0016 mole) of 2-chloroacetyl-2,3-dihydro-3-phenyl-5-chloro-1*H*-indazole (**5e**), 1 pellet of sodium hydroxide and 10 ml. of methanol was refluxed for 2 minutes, cooled and diluted with 35 ml. of water. The product was collected and recrystallized from methylene chloride-petroleum ether to yield 0.15 g. (42%) of the known indazole, m.p. and m.m.p. 125-126°.

1-Acetyl-5-chloro-3-phenylindazole (**7**).

Two g. (0.007 mole) of 2-chloroacetyl-2,3-dihydro-3-phenyl-5-chloro-1*H*-indazole (**5e**) was treated with 30 ml. of triethylamine and the reaction mixture stirred overnight at room temperature. The mother liquor was decanted from the gummy precipitate, concentrated *in vacuo* and the residue crystallized from methanol. The analytical sample was recrystallized from methylene chloride-methanol to yield 0.09 g. (5%) of colorless needles, m.p. 159-161°; ir (chloroform): 1720 cm^{-1} (C=O); uv: λ max 229 mμ (ε, 34,500), infl 238-239 (29,100), max 312-317 (14,900).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.5; H, 4.1; N, 10.3. Found: C, 66.4; H, 4.1; N, 10.5.

This compound was identical to that prepared by G. Field by acetylation of 5-chloro-3-phenylindazole (**8**) (10).

5-Chloro-3-methyl-3-phenyl-3*H*-indazole (**9b**) *via* the Sulfuric Acid Salt of 2,3-Dihydro-3-methyl-3-phenyl-5-chloro-1*H*-indazole (**6b**).

A solution of 12.0 g. (0.045 mole) of 2-(α-hydroxy-α-methylbenzyl)-4-chlorophenylhydrazine (**4b**) in 30 ml. of concentrated sulfuric acid, after standing for 2 minutes, was poured into 225 ml. of ice-water. A gum precipitated from solution, which slowly crystallized. It was collected and recrystallized from a mixture of chloroform, methanol and ether to yield 10.6 g. (69%) of the product melting at 113-117°.

The salt (7.8 g., 0.02 mole) was partitioned between 250 ml. of methylene chloride and 250 ml. of a saturated sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulfate and treated with 40 g. (0.46 mole) of manganese dioxide. The mixture was stirred at room temperature overnight. The course of the reaction could be followed using thin layer chromatography. Filtration and concentration *in vacuo* afforded 4.5 g. (80%) of colorless crystals, m.p. 54.5-57.5°. The analytical sample was recrystallized from aqueous methanol, m.p. 55-56.5°; uv: λ max 233 mμ (ε, 16,500), 270 (7,800), 350 (240).

Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.3; H, 4.6; N, 11.5. Found: C, 69.4; H, 4.6; N, 11.7.

N-[2-(α-Hydroxybenzyl)-4-chloro]anilino-2-iminopropane (**10a**).

4-Chloro-2-(α-hydroxybenzyl)phenylhydrazine (6.0 g., 0.024 mole) (**4d**) was dissolved in an excess of acetone. Compound **10a** precipitated from solution, was collected and recrystallized from methylene chloride-petroleum ether to yield 4.5 g. (65%) of colorless needles, m.p. 167-171°; ir (chloroform): 3360 cm^{-1} (OH); uv: λ max 285-287 mμ (ε, 21,386).

Anal. Calcd. for $C_{16}H_{17}ClN_2O$: C, 66.5; H, 5.9; N, 9.7; Cl, 12.3. Found: C, 66.5; H, 6.1; N, 9.6; Cl, 12.1.

N-[2-(α-Hydroxybenzyl)-4-chloro]anilino)-2-iminoethane (**10b**).

A suspension of 10.0 g. (0.04 mole) of 4-chloro-2-(α-hydroxybenzyl)phenylhydrazine (**4d**) in 150 ml. of methylene chloride was treated with 3.5 g. (0.08 mole) of acetaldehyde, and the reaction mixture stirred for 5 minutes, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Crystallization of the residue from a mixture of ether and petroleum ether yielded 8.3 g. (76%) of colorless crystals, m.p. 116-119°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 118-119°; ir (chloroform): 3370 cm^{-1} (OH); uv: λ max 280-281 mμ (ε, 21,250); nmr (deuteriochloroform): δ [1.56 (d, J = 2.5 Hz), 1.90 (d, J = 2.5 Hz) 3, CH_3CH=], 2.60-3.30 (broad s, 1, OH), 5.73 (s, 1, -CHO), 6.33-7.50 (m, 9, aromatic and olefinic H), mixture of syn and anti isomers.

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.6; H, 5.5; N, 10.2. Found: C, 65.6; H, 5.5; N, 10.1.

1-[4-Chloro-2-(α-hydroxybenzyl)phenyl]-2-ethylhydrazine (**11**).

N-([2-(α-Hydroxybenzyl)-4-chloro]anilino)-2-iminoethane (**10b**) (14.0 g., 0.05 mole) was added in portions to a suspension of 7.0 g. (0.18 mole) of lithium aluminum hydride in 500 ml. of ether. After stirring for 20 minutes at room temperature the reaction mixture was hydrolyzed by addition of water. The inorganic material was filtered and washed with ether. The filtrate was dried and evaporated. Crystallization of the residue from petroleum ether yielded 12.8 g. (92%) of product, m.p. 101-105°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 103-104.5°; ir (chloroform): 3325 cm^{-1} (OH); uv: λ max 253 mμ (ε, 10,581), 303 (2,240).

Anal. Calcd. for $C_{15}H_{17}ClN_2O$: C, 65.1; H, 6.2; N, 10.1. Found: C, 65.0; H, 6.3; N, 10.4.

5-Chloro-2-ethyl-3-phenyl-2*H*-indazole (**14**).

1-[4-Chloro-2-(α-hydroxybenzyl)phenyl]-2-ethylhydrazine (**11**) (10 g., 0.036 mole) was treated with 25 ml. of concentrated sulfuric acid. The deep blue color which formed rapidly faded. When the slightly exothermic reaction was over, the reaction mixture was poured onto ice and partitioned between methylene chloride and aqueous ammonia. The organic layer was dried and concentrated *in vacuo*. Crystallization of the oily residue from aqueous methanol gave 5.5 g. (59%) of product, m.p. 87-89°. A sample was filtered through silica gel and recrystallized from petroleum ether, m.p. 88-89.5°; uv: λ max 220 mμ (ε, 35,000), 263 (6,450), sh 290-293 (6,760), max 316 (10,100).

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.2; H, 5.1; N, 10.9. Found: C, 69.9; H, 5.1; N, 11.0.

5-Chloro-1-ethyl-3-phenylindazole (**15**).

To a solution of 1.9 g. (0.0083 mole) of 5-chloro-3-phenylindazole (**8**) in 10 ml. of dimethylformamide was added 0.5 g. (0.0103 mole) of a 56% suspension of sodium hydride in mineral oil. The mixture was stirred until the gas evolution ceased, 1.6 g. (0.0103 mole) of ethyl iodide was added and stirring continued for 1 hour at 25°. The mixture was poured into ice-water and extracted with methylene chloride. The organic layer was dried and evaporated and the residue was chromatographed over 40 g. of silica gel using methylene chloride. Crystallization of the early fractions from petroleum ether gave 1.3 g. (62%) of product, m.p. 43-48°. The analytical sample was recrystallized from aqueous methanol, m.p. 46-49°; uv: λ max 204 mμ (ε, 30,000), 223-224 (33,400), 253-254 (11,750), infl 281 (5,000), max 319-321 (9,750).

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.2; H, 5.1; N, 10.9. Found: C, 70.4; H, 5.2; N, 11.00.

Further elution with methylene chloride gave 0.15 g. (7%) of **14**, m.p. 85-87°.

6-Chloro-1-ethylideneamine-2-methyl-4-phenyl-1,2-dihydro-4*H*-3,1-benzoxazine (**12c**) and (**d**).

Acetaldehyde (50 ml.) was added to 20.0 g. (0.08 mole) of 4-chloro-2-(α-hydroxybenzyl)phenylhydrazine (**4d**). A solution formed followed by precipitation of a mixture of isomers **12c** and **d**. The acetaldehyde was allowed to evaporate and the residue was

triturated with petroleum ether and filtered to yield 16.0 g. of crude **12c**, m.p. 116-126°. Recrystallization from methylene chloride-petroleum ether gave 13.1 g. (55%) of colorless prisms, m.p. 130.5-133.5°; uv: λ max 286 mμ (ε, 16,260); nmr (deuteriochloroform): δ 1.52 (d, 3, J = 3.0 Hz, CH_3CH-), 2.10 (d, 3, J = 2.5 Hz, CH_3C=), 5.50 (q, 1, J = 3.0 Hz, C_2-H), 5.90 (s, 1, C_6H_5-CH-O) 6.70-7.36 (m, 9, aromatic and olefinic H).

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.9; H, 5.7; N, 9.3. Found: C, 67.7; H, 5.8; N, 9.2.

The petroleum ether filtrate was evaporated to afford 3.1 g. of crude **12d**; m.p. 92-96°. Fractional crystallization from ether-petroleum ether, followed by recrystallization from aqueous methanol yielded colorless prisms, m.p. 112-115°; uv: λ max 259 mμ (ε, 6,300), sh 280 (5,430); nmr (deuteriochloroform): δ 1.54 (d, 3, J = 3.0 Hz, CH_3CH-), 2.04 (d, 3, J = 2.5 Hz, CH_3-CH=), 5.05 (q, 1, J = 3.0 Hz, C_2-H), 5.80 (s, 1, C_6H_5-CH-O), 6.70-7.60 (m, 9, aromatic and olefinic H).

Anal. Found: C, 67.7; H, 5.8; N, 9.2.

4-Chloro-2-(α-hydroxybenzyl)-*N*-methyl-*N*-nitrosoaniline (**17**).

A solution of 12.4 g. (0.05 mole) of 4-chloro-2-(α-hydroxybenzyl)-*N*-methylaniline (**11**) in 150 ml. of glacial acetic acid was cooled to 5-10° with stirring. Sodium nitrite (3.5 g., 0.05 mole) dissolved in 15 ml. of water was added dropwise, and the stirring was continued for 15 minutes. The reaction mixture was poured into ice-water and partitioned between methylene chloride and aqueous ammonia. The organic layer was dried and evaporated. Crystallization of the residue from a mixture of ether and petroleum ether gave 8.1 g. (62%) of product, m.p. 65-68°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 69-71.5°; ir (chloroform): 3610 cm^{-1} (OH); uv: λ infl 219 mμ (ε, 20,700), infl 253 (7,500).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.8; H, 4.7; N, 10.1. Found: C, 60.7; H, 4.8; N, 10.2.

5-Chloro-1-methyl-3-phenylindazole 2-Oxide (**19**).

a) 4-Chloro-2-(α-hydroxybenzyl)-*N*-methyl-*N*-nitrosoaniline (**17**) (0.10 g., 0.00036 mole) was dissolved in a few drops of concentrated sulfuric acid. The solution was diluted with water and the product collected and recrystallized from methylene chloride-petroleum ether to yield 0.04 g. (43%) of colorless crystals melting at 155-160°. The analytical sample was recrystallized from the same mixture, m.p. 158-163°; uv: λ max 231-232 mμ (ε, 27,150), 246-247 (24,580), 311 (15,350).

Anal. Calcd. for $C_{14}H_{11}ClN_2O$: C, 65.0; H, 4.3; N, 10.8. Found: C, 64.9; N, 4.2; N, 10.8.

b) A solution of 31.0 g. (0.125 mole) of 4-chloro-2-(α-hydroxybenzyl)-*N*-methylaniline in 200 ml. of hydrochloric acid (37.8%) was cooled to -15° with stirring. Sodium nitrite (9.0 g., 0.13 mole) dissolved in 45 ml. of water was added dropwise and the stirring continued for 15 minutes. The mixture was poured into ice-water and extracted with methylene chloride. The organic layer was dried and evaporated, and the residue treated with 50 ml. of concentrated sulfuric acid. After standing for 5 minutes, the solution was poured into ice-water. The product was collected, washed with water and recrystallized from methylene chloride-petroleum ether to yield 9.3 g. (29%) of colorless crystals, m.p. 158-163°.

1-Acetoxymethyl-5-chloro-3-phenyl-1*H*-indazole (**18**).

5-Chloro-1-methyl-3-phenylindazole 2-oxide (**19**) (10.0 g., 0.038 mole) was refluxed in 250 ml. of acetic anhydride for 2 days. The reaction mixture was cooled, poured onto ice and made basic with aqueous ammonia. The precipitate was collected, washed with water and recrystallized from methanol (Norite) to yield 7.4 g. (65%) of colorless needles, m.p. 81-81.5°; ir (chloroform): 1750 cm^{-1} (C=O); uv: λ max 220 mμ (ε, 37,300), infl 251 (10,000), infl 257 (8,500), infl 270 (6,000), max 308-309 (9,600), infl 312-313 (9,500).

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.9; H, 4.4; N, 9.3. Found: C, 64.1; H, 4.2; N, 9.4.

3-Methyl-3-phenyl-3*H*-indazole (**9a**) and 2-Acetyl-2,3-dihydro-3-methyl-3-phenyl-5*H*-indazol-4-one (**20a**).

A mixture of 2-acetyl-2,3-dihydro-3-methyl-3-phenyl-1*H*-indazole (**5a**) (19.0 g., 0.075 mole) and 80 g. (0.92 mole) of manganese dioxide in 1 l. of methylene chloride was stirred at 25° for 45 minutes, filtered through Celite and the filtrate concentrated *in vacuo*. Addition of a mixture of ether and petroleum ether to the residue yielded 8.5 g. (43%) of **20a**; m.p. 162-168°. A sample was filtered through silica gel and recrystallized from methylene chloride-petroleum ether to give yellow prisms, m.p. 169-171°; ir (chloroform): 1700 cm^{-1} (C=O); uv: λ max 252 mμ (ε, 3,200), 374 (28,850); nmr (deuteriochloroform): δ 2.06 (s, 3, C-CH_3), 2.45 (s, 3, $\overset{O}{\overset{\|}{C}}CH_3$), 6.04 (d, 1, J_{AX} = 2 Hz, C_4-H) 6.54 (q, 1, J_{AB} = 10 Hz, J_{AX} = 2 Hz, C_6H), 6.98-7.34 (m, 6, aromatic H), 7.48 (d, 1, J_{AB} = 10 Hz, C_7-H).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.1; H, 5.2; N, 10.6.

The mother liquor was concentrated *in vacuo* and distilled in a Kugelrohr in high vacuum to yield 6.6 g. (42%) of a yellow oil **9a**, b.p. 183-210°/0.5 mm Hg; uv: λ max 220 mμ (ε, 18,380), 262 (6,420).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.4. Found: C, 80.9; H, 6.0; N, 13.4.

3,3-Dimethyl-3*H*-indazole (**9c**) and 2-Acetyl-2,3-dihydro-3,3-dimethyl-5*H*-indazol-5-one (**20b**).

Sodium methylate (3.24 g., 0.06 mole) was added to a purple solution of 8.6 g. (0.045 mole) of 2-acetyl-2,3-dihydro-3,3-dimethyl-1*H*-indazole (**5c**) in 50 ml. of methanol. The temperature rose to 42° and color turned dark brown. The reaction mixture was stirred at 25° for 30 minutes and partitioned between methylene chloride and water. The organic layer was washed with water, dried and concentrated *in vacuo*. Manganese dioxide (24 g., 0.275 mole) and 250 ml. of methylene chloride was added to the residue and the mixture stirred for 15 minutes, filtered through Celite and concentrated. The residual mixture was chromatographed on 150 g. of silica gel using 5% (v/v) ethyl acetate in methylene chloride for elution. The early fractions gave 2.7 g. (41%) of **9c**, which was distilled to yield a light yellow oil, b.p. 110-120°/0.5 mm Hg; uv: λ max 218-219 mμ (ε, 9,500), infl 226 (6,500), max 260-262 (6,150), infl 300 (840), max 346-347 (284).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found: C, 73.9; H, 6.9; N, 18.9.

Later fractions gave 1.4 g. (15%) of **20b**, which was filtered through silica gel and recrystallized from a mixture of methylene chloride and petroleum ether to give yellow prisms, m.p. 128-131°; ir (chloroform): 1690 cm^{-1} (C=O); uv: λ max 248 mμ (ε, 2,660), 373 (30,950); nmr (deuteriochloroform): δ 1.75 (s, 6, $-C(CH_3)_2$), 2.45 (s, 3, $-\overset{O}{\overset{\|}{C}}CH_3$), 6.25 (d, 1, J_{AX} = 2 Hz, C_4-H), 6.58 (q, 1, J_{AB} = 10 Hz, J_{AX} = 2 Hz, C_6-H), 7.50 (d, 1, J_{AB} = 10 Hz, C_7-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.8; H, 6.1; N, 13.9.

5-Hydroxy-3-methyl-3-phenyl-3*H*-indazole (**22**).

A suspension of 9.2 g. (0.034 mole) of 2-acetyl-2,3-dihydro-3-methyl-3-phenyl-5*H*-indazol-5-one (**20a**) in a mixture of 75 ml. of methanol and 25 ml. of 50% sodium hydroxide solution was stirred for 5 minutes to give an amber solution, which was neutralized with glacial acetic acid and diluted with 400 ml. of water. The product precipitated and was collected, washed with water and recrystallized from aqueous methanol (Norite) to yield 6.2 g. (82%) of peach colored prisms, m.p. 158-161°. The analytical sample was recrystallized from ether-petroleum ether to give tan crystals, m.p. 162-164.5°; ir (chloroform): 3580 cm^{-1} (OH); uv: λ max 237 mμ (ε, 10,950), 308 (9,300).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.4; N, 12.5. Found: C, 74.8; H, 5.6; N, 12.6.

5-Acetoxy-3-methyl-3-phenyl-3*H*-indazole (**23**).

To a solution of 1.1 g. (0.005 mole) of 5-hydroxy-3-methyl-3-phenyl-3*H*-indazole (**22**) in 20 ml. of dimethylformamide was added 0.48 g. (0.011 mole) of a 56% suspension of sodium hydride in mineral oil. The mixture was stirred at 25° for 10 minutes, 1.02 g. (0.01 mole) of acetic anhydride added and stirring continued for 10 minutes. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with water, dried, evaporated and the residue was chromatographed over 5 g. of silica gel using methylene chloride. The product was then distilled to yield 0.15 g. (12%) of an oil, b.p. 203-210°/0.65 mm Hg, which crystallized to pale yellow prisms, m.p. 83-85.5°; ir (chloroform): 1760 cm^{-1} (C=O); uv: λ max 220 mμ (ε, 18,160), 267-268 (7,330), 346 (275).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.5; H, 5.3; N, 10.6.

2-Acetyl-5-dicyanomethylene-2,3-dihydro-3-methyl-3-phenyl-5*H*-indazole (**21**).

A mixture of 9.0 g. (0.035 mole) of 2-acetyl-2,3-dihydro-3-methyl-3-phenyl-1*H*-indazole (**5a**), 13.0 g. (0.1 mole) of tetracyanoethylene and 90 ml. of ethanol was stirred at 25° overnight, filtered and the product washed with 2-propanol. Recrystallization from a mixture of methylene chloride and 2-propanol yielded 3.5 g. (32%) of brown-red needles, m.p. 197-200°; ir (chloroform): 2220 cm^{-1} (CN) 1695 (C=O); uv; λ infl 220 mμ (ε, 11,250), max 253 (5,300), 450 (34,700); nmr (deuteriochloroform): δ 2.14 (s, 3, $C\text{-}CH_3$), 2.48 (s, 3, CCH_3), 6.74-7.40 (m, 8, aromatic H); mass spectrum m/e 314 (M^+).

Anal. Calcd. for $C_{19}H_{14}N_4O$: C, 72.6; H, 4.5; N, 17.8. Found: C, 72.7; H, 4.4; N, 17.7.

Bis-(2-acetyl-2,3-dihydro-3-methyl-3-phenyl-5*H*-indazolidene) (Mixture of Isomers **24a** and **24b**).

A suspension of 9.0 g. (0.035 mole) of 2-acetyl-2,3-dihydro-3-methyl-3-phenyl-1*H*-indazole (**5a**), and 16.0 g. (0.18 mole) of manganese dioxide in 100 ml. of diethyl malonate was stirred at 25° overnight. The deep purple reaction mixture was diluted with 500 ml. of methylene chloride, filtered and concentrated *in vacuo*. The residue was crystallized from a mixture of ether and petroleum ether to yield 3.9 g. of a blue-black solid. Recrystallization from methylene chloride-petroleum ether gave 2.8 g. (32%) of purple crystals, m.p. 283-285° dec.; ir (chloroform): 1665 cm^{-1} (C=O); uv: λ max 263 mμ (ε, 5,650), 334 (5,650), 446 (4,500), 478 (23,500), 515 (278,000), 568 (9,850), 618-619 (5350); nmr (deuteriochloroform): δ 2.08 (s, 6, 2C-CH_3), 2.36 (s, 6, 2-C-CH_3), 6.80-7.50 (m, 16, aromatic H); mass spectrum m/e 500 (M^+).

Anal. Calcd. for $C_{32}H_{28}N_4O_2$: C, 76.8; H, 5.6; N, 11.2. Found: C, 76.7; H, 5.6; N, 11.2.

5,5-Bis-(3-methyl-3-phenyl-3*H*-indazole (**25**).

A mixture of 2.5 g. (0.005 mole) of bis-(2-acetyl-2,3-dihydro-3-methyl-3-phenyl-5*H*-indazolidene) **24a** and **24b**, 7.5 ml. of a 50% solution of sodium hydroxide and 30 ml. of ethanol was refluxed for 5 minutes, diluted with 160 ml. of water and neutralized with glacial acetic acid. A yellow solid (**26**) was collected, treated with 8.0 g. (0.09 mole) of manganese dioxide and 50 ml. of methylene chloride and the resulting suspension stirred at 25° for 25 minutes. The reaction mixture was filtered through Celite and evaporated. Crystallization of the residue from methanol gave a brown solid which was recrystallized from methylene chloride-petroleum ether to yield 0.4 g. (20%) of one isomer of the product, m.p. 201-208°. The analytical sample was recrystallized from methylene chloride-methanol to yield off-white crystals, m.p. 212-214°; uv: λ infl 224 mμ (ε, 27,500), max 313 (23,750); nmr (deuteriochloroform): δ 1.94 (s, 6, $2CH_3$), 7.2-8.4 (m, 16, aromatic H).

Anal. Calcd. for $C_{28}H_{22}N_4$: C, 81.1; H, 5.3; N, 13.5. Found: C, 81.1; H, 5.3; N, 13.7.

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