Reactions of Hydroxydiphenylmethyl 3-Indolyl Ketone with Grignard Reagents

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Condensation of ethyl 3-indoleglyoxylate (I) with phenylmagnesium bromide gave hydroxydiphenylmethyl 3-indolyl ketone (II). On treatment with methyllithium, II afforded 2-(3-indolyl)-1,1-diphenyl-1,2-propanediol (VII). With dimethyl sulfate, II underwent mostly *N*-alkylation to hydroxydiphenylmethyl 1-methyl-3-indolyl ketone (III), but some *O*-methylation also occurred. On treatment with an excess of methylmagnesium iodide in presence of metallic magnesium, II gave benzhydryl 3-indolyl ketone (IX) and benzhydryl 2-methyl-3-indolyl ketone (X) and an attempt was made to elucidate the nature of this reduction.

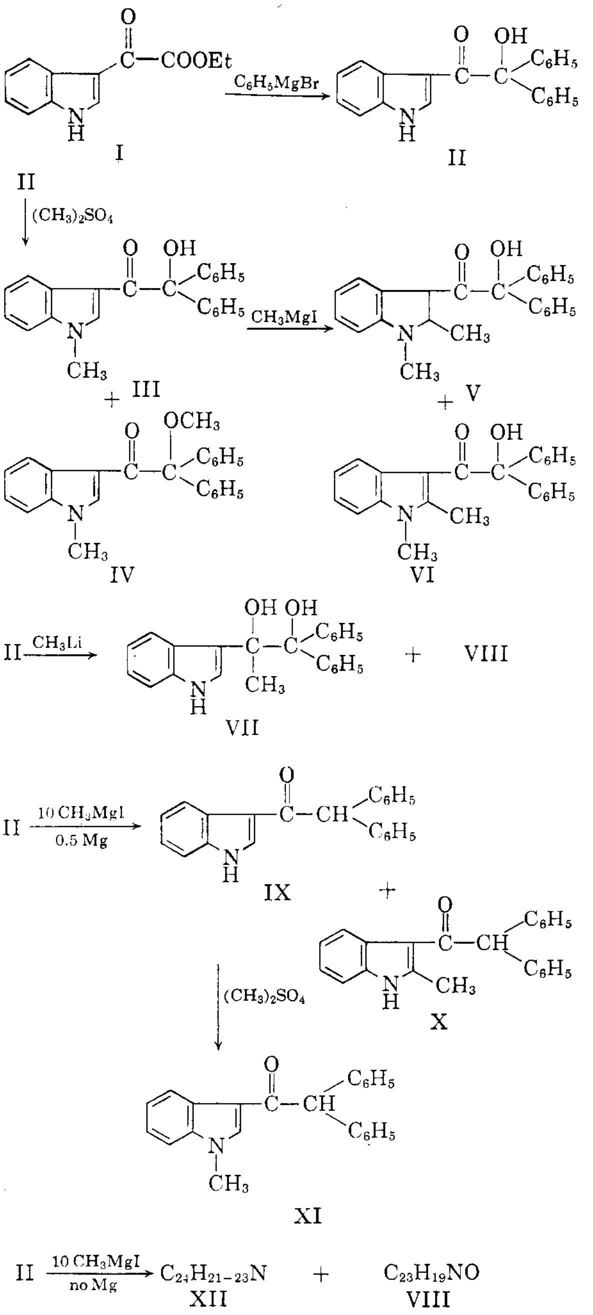
In continuation of our studies[1] on the reaction of ethyl indole-3-glyoxylate (I) with Grignard reagents we have examined the condensation of I with phenylmagnesium bromide. It was of interest to evaluate the pharmacological activity of the acyloin which would result from this reaction and also of the further transformation products of the acyloin—*e.g.*, the 1,2-diols.

When I was treated with four moles of phenylmagnesium bromide, hydroxydiphenylmethyl 3-indolyl ketone (II) was obtained in 63% yield. This compound underwent solvate formation extremely readily and afforded well defined acetone and ether complexes. The product was the acyloin II as shown by analytical data, ultraviolet and infrared spectra, formation of an oxime, reaction with methyllithium to give VII, the reduction with methylmagnesium iodide to give IX (*vide infra*).

When eight moles of phenylmagnesium bromide was used, the yield of II did not change significantly. The reaction probably stops at the stage of the acyloin because of extensive enolization and steric hindrance.

The ketone function in II was very sluggish in the reaction with hydroxylamine (see Experimental). Compound II was readily methylated with both methyl iodide and dimethyl sulfate. With the latter reagent some *O*-methylated product accompanied the expected *N*-alkylated material—hydroxydiphenylmethyl 1-methyl-3-indolyl ketone (III).

When III was subjected to reaction with methylmagnesium iodide, two compounds were isolated for which structures V and VI are proposed. Compound V gave an ultraviolet spectrum typical of an indoline (*cf.*, ref. 2, footnote 1) (λ_{max} 250; 8625 and λ_{max} 300; 3050) and the infrared indicated a saturated ketone function at 1713 cm.$^{-1}$. This product (V) was formed by 1,4-addition of the Grignard reagent, a phenomenon which we have observed previously in the case of 1-methyl-3-benzoylindole.[2] The second compound (VI) was very likely formed by dehydrogenation of V per-



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[1] J. Szmuszkovicz, *J. Org. Chem.*, **27**, 515 (1962).

[2] J. Szmuszkovicz, *J. Org. Chem.* **27**, 511 (1962).

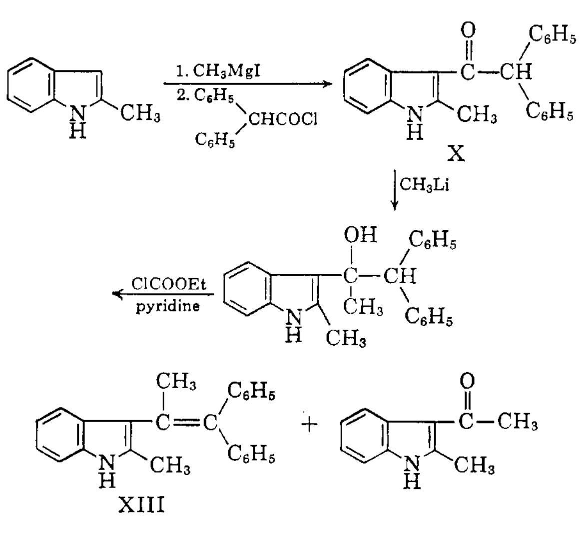
haps during chromatography, as we have previously demonstrated that this type of transformation occurs very readily in the case of 1-methyl-2-phenyl-3-benzoylindoline.[2]

When acyloin II was treated with methyllithium, the 1,2-product, 2-(3-indolyl)-1,1-diphenyl-1,2-propanediol (VII), was obtained in 51% yield. A companion compound, $C_{23}H_{19}NO$(VIII), of unknown structure was also isolated.

Reaction of the glyoxylate II with methylmagnesium iodide was tried initially under the usual conditions, namely the reagent was prepared from ten equivalents of methyl iodide and 10.5 equivalents of magnesium. Subsequently it was found that the 0.5-equivalent excess of metallic magnesium was quite critical with regard to obtaining the unusual reduction phenomenon which led to benzhydryl 3-indolyl ketone (IX) in 63% yield. Compound IX was also prepared for comparison from indole, *N*,*N*-dimethyldiphenylacetamide, and phosphorus oxychloride and the two samples were identical.

A second product, obtained in 4.2% yield from the reaction of II with methylmagnesium iodide in the presence of excess magnesium proved to be benzhydryl 2-methyl-3-indolyl ketone (X). The structure was unequivocally established by an independent synthesis from 2-methylindole, methylmagnesium iodide, and diphenylacetyl chloride.

Six experiments were conducted in order to determine the nature of the reducing agent in the conversion of II → IX. In the first of these experiments II was treated with ten equivalents of methylmagnesium iodide in the absence of metallic magnesium, and two products were isolated. The first compound (VIII) was identical with the compound (structure unknown) obtained from the reaction of II with methyllithium. The second product (XII, $C_{24}H_{21-23}N$) likewise eluded structural elucidation. Although the spectral properties of XII are consistent with 2-methyl-3-(1-methyl-2,2-diphenylvinyl)indole (XIII), synthesis of XIII by the route formulated below and comparison of the two specimens proved them non-identical. It is interesting to note that during the dehydration with ethylchloroformate in pyridine[3] some elimination occurred to give 2-methyl-3-acetylindole.



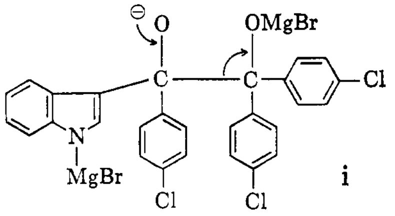
X

XIII

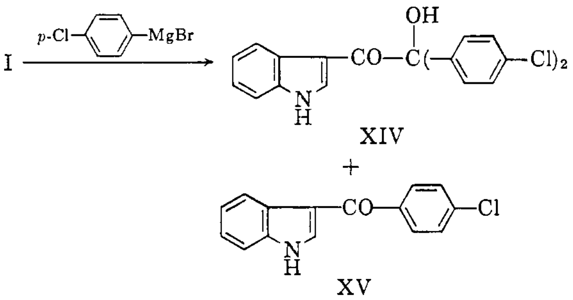
Only starting material was obtained when II was treated with the following reagents: methylmagnesium chloride, magnesium iodide, magnesium subiodide,[4] and magnesium subiodide in the presence of triethylamine and also in presence of two equivalents of methylmagnesium iodide. The last three experiments were performed in presence of metallic magnesium.[5]

Alkylation of IX with dimethyl sulfate afforded benzhydryl 1-methyl-3-indolyl ketone (XI) in 98% yield.

Reaction of I with *p*-chlorophenylmagnesium bromide gave bis(*p*-chlorophenyl)-hydroxymethyl 3-indolyl ketone (XIV) and a small amount of an elimination[6] product which, on the basis of spectral and analytical data, is 3-(*p*-chlorobenzoyl)indole (XV).



i



XIV

XV

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[3] G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **74**, 5454 (1952).

[4] M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

[5] We do not have a satisfactory mechanism which would take into account all the experimental facts mentioned above, but clearly the presence of metallic magnesium is essential for the transformation II → IX and it is likely that a free radical process is involved. A number of other examples of reduction with methylmagnesium iodide have been reported and summarized: M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice Hall, New York, 1954, p. 189. See also the reduction in presence of cuprous iodide reported by U. Ghatak, N. N. Saha, and P. C. Dutta, *J. Am. Chem. Soc.*, **79**, 4487 (1957).

[6] This elimination probably occurs *via* the intermediate and should also give rise to *p,p*,-dichlorobenzhydrol which we did not attempt to isolate.

Experimental[7,8]

Hydroxydiphenylmethyl 3-Indolyl Ketone (II).—A solution of ethyl indole-3-glyoxylate (I. 173.80 g., 0.8 mole) in 3 l. of tetrahydrofuran was added to a solution of phenylmagnesium bromide [prepared from 502.4 g. (3.2 moles) of bromobenzene and 81.60 g. (3.36 g.-atoms) of magnesium in 2400 ml. of ether] with stirring during 70 min. The resulting suspension was then heated at reflux temperature for 2 hr. and allowed to stand overnight. It was cooled in ice and decomposed with a solution containing 428 g. of ammonium chloride in 2 l. of water. The aqueous layer was extracted with ether (3 × 200 ml.) and the combined organic solution was washed with water, dilute sodium thiosulfate solution, water, then with saturated salt solution, and dried through sodium sulfate. Evaporation at 40° *in vacuo*[9] afforded a yellow solid which was crystallized from 200 ml. of methanol to give 168.0 g. of rods melting at 143–149°. The filtrate was evaporated to dryness and the resulting dark oil treated with 150 ml. of ether whereupon a precipitate was obtained, 30.40 g., m.p. 99° (efferv., probably as ether solvate). The two crops were combined and recrystallized from 150 ml. of methanol to give 155.7 g. of colorless material melting at 151–153°. The second crop amounted to 9.34 g. of the same melting point (63% yield).

For analysis the compound was recrystallized from methanol, m.p. 155–156°. Ultraviolet spectrum showed λ_{max} 246 (14,700); 264 (10,200); 308 (13,325). In 0.01 *N* alcoholic KOH: 246 (11,825); 267 (12,150); f 276 (8975); 310 (10,325), 340 (6525). Infrared spectrum showed NH, OH: 3370, 3300; C=O: 1590; C=C: 1575, 1560, 1488.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71 H, 5.24; N, 4.28. Found: C, 80.55; H, 5.31; N, 4.34.

This acyloin undergoes solvate formation very easily. It can be crystallized from acetone to give rods, m.p. (taken on finely ground sample) 151.5–153° (s 92°).

Anal. Calcd. for $C_{22}H_{17}NO_2$ + CH_3COCH_3: C, 77.90; H, 6.01; N, 3.63; active H, 2. Found: C, 78.28; H, 6.01; N, 3.53; active H, 2.3.

The infrared spectrum showed typical acetone bands at 1697, 1357, and 1217 cm.$^{-1}$ which were not present in the anhydrous material and effectively disappeared on thorough drying at 100° in 0.1 mm.

Mere washing of the crystalline material with ether or recrystallization from benzene–ether produced an ether solvate as needles, m.p. 96–98° (efferv.), resolid. 108°, remelts 145–146°.

Anal. Calcd. for $C_{22}H_{17}NO_2 \cdot 1/2C_4H_{10}O$: C, 79.09; H, 6.09; N, 3.84; 0, 10.98. Found: C, 79.31; H, 5.88; N, 3.50; O, 11.27.

Hydroxydiphenylmethyl 1-Methyl-3-indolyl Ketone (III). A. With Sodium Methoxide and Methyl Iodide.—Hydroxydiphenylmethyl 3-indolyl ketone acetone solvate (1.90 g., 4.94 mmoles) was added to a solution of sodium (0.58 g., 25 mg.-atoms) in 20 ml. of methanol. The solution was refluxed for 15 min. and allowed to cool to room temperature. Methyl iodide (1.55 ml., 25 mmoles) was added and the solution refluxed for 70 min. During this time a considerable amount of crystalline precipitate formed. The mixture was cooled, 1 ml. of methyl iodide added, and refluxing continued for 2 hr. The mixture was evaporated to dryness, cooled, and 50 ml. of water was added. The precipitate was filtered, washed with water, and crystallized from about 50 ml. of methanol to give 1.10 g. melting at 175–178° (s 172°). The second crop amounted to 0.28 g., m.p. 172–174° (yield 82%).

The analytical sample was prepared by two recrystallizations from methanol, m.p. 176.5–179°. Ultraviolet spectrum showed λ_{max} 249 (15,775); f 264 (9825); 312 (15,750). No change in alkali. Infrared spectrum showed OH: 3420; C=O: 1630 sh, 1612; C=C: 1575, 1513.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.27; H, 5.89; N, 4.06.

B. With Dimethyl Sulfate and Alkali in Acetone.[10]—A solution of hydroxydiphenyl-methyl 3-indolyl ketone (as one-half ether solvate; 3.27 g., 0.009 mole) in 100 ml. of acetone was added to a solution of potassium hydroxide (11.20 g., 0.2 mole) in 50 ml. of water. Dimethyl sulfate (9.5 ml., 0.1 mole) was added to the resulting solution during 10 min. and the reaction mixture was stirred for another 30 min. Acetone was then evaporated *in vacuo* at 50° and the resulting suspension was filtered. The product was washed with water and crystallized from *ca.* 100 ml. of methanol to give leaflets; 2.1 g. (66% yield), m.p. 176–179°. Mixed melting point with the sample obtained by the methyl iodide–sodium methoxide procedure showed no depression. The filtrate was evaporated to *ca.* 40 ml. to give an ill-defined solid; 0.35 g., m.p. 105–110°. Crystallization from methanol afforded prisms (0.25 g.) melting at 128–130°. Two further recrystallizations gave methoxydiphenylmethyl 1-methyl-3-indolyl ketone (IV) melting at 128–129°. Ultraviolet spectrum showed λ_{max} 208 (44,500); 250 (15,100); f 264 (8550); 315 (16,100). No change in alkali. Infrared spectrum showed no OH, NH; C=O: 1630; C=C: 1615, 1600, 1575, 1515, 1495, 1485; C—O C—N: 1363, 1210, 1183, 1170, 1127, 1098, 1088, 1077.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94; OCH_3, 8.73; active H, 0. Found: C, 80.63; H, 6.15; N, 3.73; OCH_3 (gravimetric), 8.49; active H, 0.14.

Oxime of II.—A mixture of II (2.30 g., 7 mmoles), hydroxylamine hydrochloride (4.85 g., 70 mmoles), and 15 ml. of pyridine was heated on the steam bath for 15 hr. The resulting yellow solution was cooled in ice and 80 ml. of water was added. The oil obtained solidified on scratching and cooling for 2 hr. The solid was filtered and washed with water; 2.30 g., m.p. 115–135°. It was refluxed with 30 ml. of benzene, filtered while hot, and the insoluble precipitate washed with benzene; 0.35 g., m.p. 215–220° (fast). The oxime was recrystallized from methanol to give small prisms, m.p. 215–216.5° unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} f 260 (5425); f 272 (7275); 279 (7475); 288 (6925). No change in alkali. Infrared spectrum showed OH, NH: 3360 sh, 3280 sh, 3200; C=N: 1673 sh, 1655, 1632; C=C: 1598 sh, 1580, 1517, 1496.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.89; H, 5.56; N, 7.96.

The original benzene filtrate was treated with Magnesol, filtered, and evaporated to *ca.* 10 ml. and allowed to crystallize during a few days to give ill-defined crystals (1.45 g.) melting 125–180°. Treatment with boiling benzene as before gave an additional 0.10 g. (total yield 18.8%) of the oxime melting at 214–215°. Dilution of the filtrate with an equal volume of ether afforded 1.0 g. of the starting material as the solvate.

The Reaction of III with Methylmagnesium Iodide.—A solution of hydroxydiphenylmethyl 1-methyl-3-indolyl ketone (2.10 g., 6.15 mmoles) in 50 ml. of benzene was addded during 5 min. to a solution of methylmagnesium iodide prepared from methyl iodide (3.85 ml., 61.6 mmoles) and magnesium (1.57 g., 64.5 mg.-atoms) in 50 ml. of ether. The mixture was refluxed with stirring for 21 hr., and worked up as before[9] to give 2.10 g. of an amorphous solid. It was dissolved

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[7] Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary spectrophotometer Model 14. Infrared spectra (recorded in cm.$^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is a magnesia–silica gel adsorbent manufactured by Floridin Co., Tallahassee, Fla.

[8] The author is indebted to Professors D. J. Cram and M. S. Newman for stimulating discussions, to Mr. W. A. Struck and his associates for microanalyses, to M. F. Grostic and Mr. J. E. Stafford for infrared and ultraviolet spectra, and to Mr. L. G. Laurian for laboratory assistance.

[9] This type of work-up was used throughout the Experimental.

[10] *Cf.*, C. B. Barrett, R. J. S. Beer, G. M. Dodd, and A. Robertson, *J. Chem. Soc.*, 4810 (1957).

in 10 ml. of benzene and chromatographed on 60 g. of Florisil. Elution with 450 ml. of 1% acetone–Skellysolve B gave oily fractions which were discarded. Further elution with 1050 ml. gave solid fractions ranging in m.p. from 135° to 144° (1.35 g., 61.5% yield). Four crystallizations from ether–Skellysolve B afforded hydroxydiphenylmethyl 1,2-dimethyl-3-indolinyl ketone (V) as clusters melting at 144.5–145.5°. Ultraviolet spectrum showed λ_{max} 250 (8625); 300 (3050). No change in alkali. Infrared spectrum showed OH: 3145 sh, 3040; C═O: 1713; C═C: 1600, 1495, 1482; C—O, C—N: 1250; ring. 805, 753 sh, 745, 708, 687.

Anal. Calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.93; C—CH$_3$, 4.2; N.E. 357.43. Found: C, 80.90; H, 6.62; N, 3.93; C—CH$_3$, 3.4; N.E. 347.

Further elution with 1500 ml. of 1% acetone–Skellysolve B gave only oily fractions. Elution with 150 ml. of acetone gave 0.70 g. of material which was crystallized from ether–Skellysolve B to give 0.16 g. of VI as yellow prisms, m.p. 217–219°. Recrystallization from benzene (Magnesol) gave pale green prisms melting at 219.5–221.5°. Ultraviolet spectrum showed λ_{max} 212 (42,975); 253 (11,225); 272 (8375); 314 (11,750). No change in alkali. Infrared spectrum showed OH: 3545; C═O: 1655 sh, 1640; C═C: 1605, 1505, 1495; C—O, C—N: 1102, 1082, 1052, 1030; ring: 830, 762, 750, 733, 723, 709, 692, 658.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.05; H, 6.39; N, 3.94.

2-(3-Indolyl)-1,1-diphenyl-1,2-propanediol (VII).—A solution of methyllithium[11] was prepared from 12.5 ml. (0.2 mole) of methyl iodide and 3.06 g. (0.44 g.-atom) of lithium wire in 150 ml. of ether. It was added under nitrogen during 10 min. to a stirred solution of hydroxydiphenylmethyl 3-indolyl ketone (6.54 g., 0.02 mole) in 200 ml. of benzene. The mixture was refluxed for 2 hr.

The initially formed precipitate dissolved and the green solution finally turned dark brown. The solution was worked up as before[9] but using water for decomposition and benzene for extraction. The resulting amorphous solid (7.20 g.) was dissolved in 7 ml. of benzene and chromatographed on 220 g. of Florisil. Elution with 1 l. of 5% acetone–Skellysolve B gave 0.22 g. of an oil which was discarded. Further elution with 1 l. of the same solvent gave 0.68 g. of yellow solid ranging in m.p. from 192°–198.5°. It was triturated with ether to give 0.52 g. of colorless solid melting at 197–198.5°. Crystallization from benzene gave small needles, m.p. 198–198.5°, unchanged on further crystallization. This compound (VIII, structure unknown) was identical with the sample prepared from II and methylmagnesium iodide in the absence of magnesium. Ultraviolet spectrum showed λ_{max} 220 (34,200); 266 (11,000); pl 281 (9300). No change in alkali. Infrared spectrum showed NH, OH: 3520, 3280; band at 1638 (m); C═C: 1600, 1575, 1540, 1500; C—O: 1250, 1035 sh, 1020, 1015, ring: 776, 755, 732, 710, 680.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84,89; H, 5.89; N, 4.30. Found: C, 84.86; H, 6.00; N, 4.12.

Further elution with 3250 ml. of 5% acetone–Skellysolve B gave 5.23 g. of solid which melted at 78° (efferv.). It was crystallized from chloroform to give 3.47 g. (51% yield) of VII melting at 89° (efferv.). Recrystallization from benzene afforded clusters of needles, m.p. 105° (efferv.), unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} 220 (40,385); 281 (6100); 289 (5275). No change in alkali. Infrared spectrum showed OH, NH: 3550 sh, 3490, 3380; C═C: 1605, 1542, 1500, 1470; C—O: 1195, 1175, 1125.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.66; H, 6.35; N, 4.26.

Further elution with 1 l. of the same solvent gave 0.65 g. of an oil which could not be crystallized.

Benzhydryl 3-Indolyl Ketone (IX) by reduction of II.—A solution of hydroxydiphenylmethyl 3-indolyl ketone (as one-half ether solvate, 37.30 g., 0.107 mole) in 1 l. of benzene was added during 30 min. to a solution of methylmagnesium iodide prepared from 62.5 ml. (1 mole) of methyl iodide, 25.60 g. (1.05 g.-atoms) of magnesium in 1 l. of ether. Ether was then evaporated and the resulting mixture refluxed for 5 hr., and worked up as before[9] but using methylene chloride for extraction. The resulting solid (29.0 g.) upon trituration with ether afforded 20.59 g. (62% yield) of benzhydryl 3-indolyl ketone as colorless material melting at 187–188.5°. Crystallization from methanol raised the m.p. to 190.5–191.5°, unchanged on further recrystallization. This compound was identical with the sample prepared from *N,N*-dimethyldiphenylacetamide, indole and phosphorus oxychloride[12] (ultraviolet and infrared spectra, mixed melting point). Ultraviolet spectrum showed λ_{max} 224 (15,400); 260 (11,000) 303 (14,300); in 0.01 *N* alcoholic potassium hydroxide: 244 (13,600); 264 (11,600); 303 (12,900); 336 (4300). Infrared spectrum showed NH: 3150 sh, 3100; C═O: 1608; C═C: 1578, 1520, 1495.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; active H, 2. Found: C, 85.31; H, 5.84; N, 4.34; active H, 2.11.

The original filtrate was concentrated to a small volume, and the resulting brown material was filtered and washed with ether to give 1.47 g. (4.2% yield) of a pale yellow solid, benzhydryl 2-methyl-3-indolyl ketone (X), m.p. 190–199°. It was crystallized from methanol as clusters of colorless needles; m.p. 203–204.5° (1.06 g.) unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} 247 (12,800); 270 (10,900); 308 (14,000). No change in alkali. Infrared spectrum showed NH: 3250; C═O: 1615; C═C: 1580, 1525, 1492, 1482.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.86; H, 5.89; N, 4.30; active H, 1. Found: C, 84.76; H, 5.87; N, 4.44; active H, 1.25.

This compound was identical with an authentic sample of X prepared as described in a later section of the Experimental.

Treatment of II with Reducing Agents. A. With 10 Equivalents of Methylmagnesium Iodide in Absence of Metallic Magnesium.—A solution of methylmagnesium iodide was prepared from 17.0 g. (0.12 mole) of methyl iodide and 2.43 g. of magnesium (0.1 g.-atom) in 100 ml. of ether. Benzene (100 ml.) was added to the clear solution (free of magnesium) and the excess methyl iodide and ether was evaporated. A solution of II (3.27 g., 0.01 mole) in 100 ml. of benzene was added at room temperature and the mixture was refluxed with stirring for 6 hr. A dark yellow solution resulted with a layer of oily solid on the upper side of the flask. The mixture was worked up as before[9] but using benzene for extraction. The resulting amorphous solid was dissolved in 10 ml. of methanol and allowed to stand in the refrigerator for 2 days to give prisms (1.44 g.), m.p. 154–155°. The second crop was obtained by evaporating the filtrate down to *ca.* 5 ml. and adding 15 ml. of ether (seeding). After refrigeration overnight, 0.69 g. of material was obtained, m.p. 150.5–152.5°. The filtrate was evaporated to dryness and the residue was dissolved in 5 ml. of ether and allowed to crystallize in the cold during one day to give 0.14 g. melting at 146–150°. Mixed melting point of these three crops with the starting material showed no depression. Recovery: 1.97 g. (60% yield).

The final filtrate was evaporated to dryness to give a solid (1.21 g.), m.p. 70–85°. It was dissolved in 5 ml. of benzene and chromatographed on 36 g. of Florisil. Elution with 1% acetone–Skellysolve B (500 ml.) gave 0.21 g. of solid (XII) which was crystallized from ether–petroleum ether (30–60°) as clusters of needles, m.p. 165–165.5° (s 161°). Recrystallization raised the m.p. to 166.5–167°. Ultraviolet spectrum showed λ_{max} 227 (35,000); 284 (12,500); 290 (12,700). Infrared spectrum showed NH: 3400; C═C: 1620 sh, 1610, 1595, 1575, 1560, 1492; ring: 782, 770, 737, 700, 695.

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[11] D. A. van Dorp and J. F. Arens, *Rec. trav. chim.*, **65**, 338 (1946).

[12] W. C. Anthony, unpublished results.

Anal. Calcd. for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30; 2 C—CH_3, 9.24. Calcd. for $C_{24}H_{21}N$: C, 89.12; H, 6.55; N, 4.33; 2 C–CH_3, 9.66. Found: C, 88.70; H, 6.81; N, 4.29; C–CH_3, 8.04, 6.40, 6.15.

Further elution with 3% acetone–Skellysolve B (2500 ml.) gave 0.84 g. of solid which was crystallized from methanol (with considerable loss) to give crystals of VIII melting at 197–198°. Recrystallization from methanol afforded colorless needles, m.p. 197.5–198°. This compound is identical with the sample obtained from the reaction of II with methyllithium (ultraviolet and infrared spectra, mixed melting point).

B. With Methylmagnesium Chloride.—The solution of II (3.27 g.; 0.01 mole) in 100 ml. of benzene was added to a solution of methylmagnesium chloride (0.1 mole, free of magnesium) from which the ether had been evaporated and displaced by benzene. The reaction mixture was refluxed for 5 hr.

Work-up in the usual way afforded 2.57 g. (79% yield) of starting material.

C. With Magnesium Iodide.—A solution of II (0.01 mole) in 80 ml. of benzene was added to a solution of magnesium iodide prepared from 0.01 mole of magnesium and 0.01 mole of iodine in 50 ml. of ether and 20 ml. of benzene. The mixture was boiled for 3.5 hr. and worked up as usual to give 99.5% of recovered starting material.

When the reaction was run with 0.01 mole of the acyloin in 100 ml. of benzene and 0.05 mole of magnesium iodide and the ether was evaporated and replaced with benzene (50 ml.) prior to the addition of the acyloin, the recovery of starting material was 74%.

D. With Magnesium Subiodide.[4]—Magnesium subiodide was prepared from magnesium (2.43 g., 0.1 mole), iodine (6.80 g., 0.0269 mole), ether (16 ml.), and benzene (24 ml.). The acyloin (II) (3.27 g., 0.01 mole) was added in 50 ml. of benzene and the mixture refluxed for 4 hr. with stirring. Work-up in the usual way afforded 3.16 g. (97%) of recovered starting material.

E. With Magnesium Subiodide in Presence of Triethylamine.—A solution of II (0.01 mole) in 100 ml. of benzene containing 0.02 mole of triethylamine was added to magnesium subiodide prepared as described under D. After a 4-hr. reflux period and work-up, 97.5% yield of recovered starting material was obtained.

F. With Magnesium Subiodide in Presence of 2 Equivalents of Methylmagnesium Iodide.—When the reaction was run as described under E, but using 0.02 mole of methylmagnesium iodide in 15 ml. of ether in place of triethylamine, 99.5% recovery of the starting material was obtained.

Benzhydryl 1-Methyl-3-indolyl Ketone (XI).—A solution of benzhydryl 3-indolyl ketone (6.22 g., 0.02 mole) in 200 ml. of acetone was added to a solution of potassium hydroxide (22.40 g., 0.4 mole) in 100 ml. of water. Dimethyl sulfate (19 ml., 0.2 mole) was added during 10 min. and the solution was stirred for 0.5 hr. Acetone was evaporated *in vacuo* at 50° and the resulting suspension was cooled and filtered. The precipitate was washed well with water to give 6.40 g. (98% yield) of a colorless solid melting at 150–155°. Two crystallizations from methanol raised the melting point to 154.5–156°. Ultraviolet spectrum showed λ_{max} 247 (16,350); f 252 (15,600); f 264 (9500); 308 (16,450). In 0.01 *N* alcoholic potassium hydroxide: 247 (13,775); f 252 (12,950), f 264 (7975); 307 (13,975). Infrared spectrum showed C=O: 1635; C=C: 1610 sh, 1600 sh, 1575, 1525, 1495.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 8.84; H, 5.75; N, 4.24; OCH_3, O.

Bis(*p*-chlorophenyl)hydroxymethyl 3-Indolyl Ketone (XIV).—A solution of ethyl indole-3-glyoxylate (10.86 g., 0.05 mole) in 200 ml. of warm tetrahydrofuran was added during 25 min. to a solution of *p*-chlorophenylmagnesium bromide, prepared from *p*-chlorobromobenzene (38.30 g.; 0.2 mole), and magnesium (5.10 g., 0.21 mole) in 150 ml. of ether. The mixture was refluxed for 3 hr. and 15 min. and worked up as before.[9] The resulting brown oily residue was steam distilled until about 700 ml. of distillate was collected. The pot mixture was extracted with methylene chloride (5 × 100 ml.), washed with saturated salt solution, dried over sodium sulfate, and evaporated to give 19.4 g. of a yellow solid which was dissolved in 35 ml. of benzene and chromatographed on 510 g. of Florisil. Elution with 8200 ml. of 3% acetone–Skellysolve B gave an oil which was discarded. Further elution with 10 l. of the same solvent gave 11.25 g. of solid material which was crystallized from benzene (Magnesol) to give 8.80 g. (44.5% yield) of XIV as rods melting at 168.5–169.5° and unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} (16,550); 264 (11,275); 310 (14,625). In 0.01 *N* alcoholic potassium hydroxide: f 244 (10,975); 268 (14,450); f 276 (11,375); 312 (10,250); 342 (9150). Infrared spectrum showed OH, NH: 3400, 3300; C=O: 1602; C=C: 1575, 1510, 1487; C—O, C—N: 1333, 1238, 1155, 1140 sh, 1133, 1090, 1048, 1012, 955.

Anal. Calcd. for $C_{22}H_{15}Cl_2NO_2$: C, 66.66; H, 3.81; Cl, 17.89; N, 3.53. Found: C, 66.65; H, 3.97; Cl, 17.86; N, 3.66.

Further elution with 3,200 ml. of 5% acetone–Skellysolve B and crystallization of the solid (2.67 g.) from benzene gave 0.11 g. of XV melting at 237–239°. Two recrystallizations from ethyl acetate raised the m.p. to 241–241.5°. Ultraviolet spectrum showed λ_{max} 251 (19,800); broad f 268 (13,200); 316 (13,000). In 0.01 *N* alcoholic potassium hydroxide: 251 (17,100); f 268 (13,100); broad f 329 (10,400). Infrared spectrum showed NH: 3100; C=O 1592; C=C: 1570, 1555, 1510, 1487.

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94; Cl, 13.87. Found: C, 70.37; H, 4.45; Cl, 13.97.

Synthesis of XIII.—A. Benzhydryl 2-Methyl-3-indolyl Ketone (X).—A solution of 2-methylindole (65.50 g., 0.5 mole) in 100 ml. of benzene was added with stirring during 20 min. to a solution of methylmagnesium iodide (0.5 mole) in 125 ml. of ether in an atmosphere of nitrogen and the mixture was refluxed for 1 hr. A solution of crude diphenylacetyl chloride[13] (115.50 g., 0.5 mole) in 1 l. of benzene was added, the mixture was refluxed for 1 hr. and allowed to stand overnight. A solution of 65 ml. of acetic acid in 195 ml. of water was added with ice cooling. The resulting suspension was filtered and the oily solid was washed with ether (4 × 250 ml.) to give a brown solid. The product was crystallized from about 2 l. of ethanol and afforded 70.80 g. (in two crops) of X as colorless needles; m.p. 204–205°, unchanged on recrystallization. Yield: 43.7%. This compound was identical with the sample obtained previously as a by-product from the reaction of II with methylmagnesium iodide and magnesium (ultraviolet and infrared spectra; C, H, N analysis and mixed melting point).

B. α-Diphenylmethyl-α,2-dimethylindole-3-methanol.—A solution of methyllithium[11] (0.295 mole in 340 ml. of ether) was added during 20 min. to a stirred solution of X (16.2 g., 0.05 mole) in 500 ml. of benzene and 50 ml. of dioxane in an atmosphere of nitrogen. The resulting suspension was refluxed for 2 hr. and worked up as before[9] but using water for decomposition and benzene for extraction.

The resulting brown oil was dissolved in ether whereupon crystallization commenced immediately. The resulting solid was filtered and washed well with ether; 5.1 g., m.p. 186–196°. Crystallization from methanol afforded 2.38 g. of X (determined by mixed melting point) melting at 203–204°. The ethereal filtrate crystallized after standing overnight at room temperature to give 1.84 g. of the desired product as rods melting at 151–154°. Two recrystallizations from ether followed by two recrystallizations from methanol raised the m.p. to 157–158°. Ultraviolet spectrum showed λ_{max} 224 (38,350); sh 276 (5950); 283.5 (6650); 291 (6350). No change in base. Infrared spectrum showed OH, NH:

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[13] D. Libermann and L. Hengl, *Bull. soc. chim. France* [5], **18**, 974 (1951).

3540, 3400; ═CH: 3020, 2990; C═C; 1598, 1580, 1553, 1498, 1495; C═O: 1115; ring: 745, 737, 725, 700, 688.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10; active H, 2. Found: C, 84.20; H, 6.99; N, 4.26; active H, 2.01.

C. Dehydration to XIII.—Ethyl chloroformate[8] (5 ml.) was added during 5 min. to an ice-cooled and stirred solution of α-diphenylmethyl-α,2-dimethylindole-3-methanol (1.14 g., 3.35 mmoles) in 14 ml. of pyridine. The thick suspension was kept in ice for 1 hr. and then allowed to stand at room temperature for 7 hr. The resulting solution was treated with ice (5 g.) and water (10 ml.) and extracted with ether (3 × 50 ml.). The extracts were washed with water, saturated salt solution, dried through sodium sulfate and evaporated to give 1.40 g. of a yellow oil. It was purified by evaporative distillation at 120–160° (0.01 mm.) to give a yellow solid melting at 132–137°. Sublimation at 120–150° (0.01 mm.) afforded a mixture of products which was purified by crystallization from ether; small prisms (0.10 g.), m.p. 199.5–200.5°. This product proved identical with an authentic sample of 2-methyl-3-acetylindole[14] (ultraviolet and infrared spectra; C, H, N analysis and mixed melting point).

The first ethereal filtrate was diluted with 10 ml. of petroleum ether (b.p. 30–60°), evaporated to remove ether and allowed to crystallize; 0.20 g., m.p. 133–136°. One recrystallization from ether–petroleum ether afforded XIII as clusters of small rods, m.p. 138–139°, unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} 222 (40,500); sh 260 (8400); sh 267 (9600); 274 (10,200); sh 280 (9900); sh 290 (8100). Infrared spectrum showed OH, NH: 3380, 3300; C═C: 1628, 1605, 1585, 1552, 1497; ring: 773, 755, 750, 735, 725, 710, 703.

Anal. Calcd. for $C_{24}H_{21}N$: C, 89.12; H, 6.55; N, 4.33. Found: C, 89.12; H, 6.62; N, 4.62.

Mixed melting point of XIII with the unknown XII (m.p. 166.5–167°) was 120–124°.

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Oxidative Coupling and Cross-Coupling of Acetylenic Amines and Acetylenic Carbinols[1]

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A number of conjugate diacetylenic 1,6-amino alcohols, $R^1R^2C(NR^3R^4)—C{\equiv}C—C{\equiv}C—C(OH)R^5R^6$, and diacetylenic 1,6-diamines, $R^1R^2C(NR^3R^4)—C{\equiv}C—C{\equiv}C—C(NR^3R^4)R^1R^2$, were prepared by oxidative coupling reactions. The products absorbed three moles of hydrogen rapidly (with Raney nickel in ethanol), the fourth mole slowly. Hydrogenolysis, particularly of the carbon-nitrogen bond, occurred extensively where steric hindrance was severe.

Methods have now been described for the preparation of a remarkably varied assortment of acetylenic amines of the type $R^1R^2C(NR^3R^4)$-$C{\equiv}CH$ (A). The long list of such compounds ranges from the simplest example, propargylamine[3,4] (all R's = H), through many fully alkylated homologs[5] (all R's = alkyl), including all intermediate states of substitution.[4–7] Thus one may have these compounds with primary, secondary, or tertiary nitrogen on primary, secondary, or tertiary carbon. The corresponding acetylenic carbinols, $R^5R^6C(OH)$-$C{\equiv}CH$ (B), are well known in many primary, secondary, and tertiary modifications (R's = H and/or alkyl).

Since a few preliminary experiments[8] indicated that acetylenic amines (A) undergo oxidative cross-coupling with acetylenic carbinols (B), we have studied the reaction in greater detail to provide a sterically varied group of new conjugate diacetylenic 1,6-amino alcohols (C) and related compounds for physiological screening.[9]

$$\underset{(A)}{R^1R^2C(NR^3R^4)—C{\equiv}CH} + \underset{(B)}{R^5R^6C(OH)—C{\equiv}CH} \rightarrow$$

$$\underset{(C)}{R^1R^2C(NR^3R^4)—C{\equiv}C—C{\equiv}C—C(OH)R^5R^6}$$

$$+ \underset{(D)}{[R^1R^2C(NR^3R^4)—C{\equiv}C—]_2} + \underset{(E)}{[R^5R^6C(OH)—C{\equiv}C—]_2}$$

The oxidative coupling[10] and cross-coupling[11] of terminal acetylenes has long been known. The more recent discovery of many polyacetylenes among natural products has revived interest in these reactions, now often used in the synthesis of such substances.[12,13]

The oxidative coupling procedure described by Zalkind[14,15] was selected for our purpose. Use of

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(1) Paper No. 77 on substituted acetylenes; previous paper, G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).

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