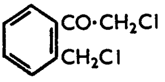
122. *The Interaction of* o-*Chloromethylphenacyl Chloride and Primary Amines: a Novel Formation of the* iso*Indoline System.*

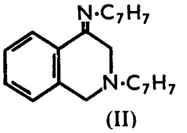
By I. G. HINTON, FREDERICK G. MANN, and A. VANTERPOOL.

o-Chloromethylphenacyl chloride has been prepared by the action of diazomethane on *o*-chloromethylbenzoyl chloride, in order that, by reaction with aniline, it might afford 1 : 2 : 3 : 4-tetrahydro-4-oxo-2-phenyl*iso*quinoline. It condenses, however, with aniline in neutral or weakly basic solution to give 3-methyl-2-phenyl-1-phenylimino*iso*indoline. The *m*-tolyl and *p*-tolyl analogues have been similarly prepared.

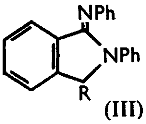
BEFORE our successful synthesis of 2-substituted 1 : 2 : 3 : 4-tetrahydro-4-oxo*iso*quinolines,[1] another route was investigated with unexpected results. For this synthesis, we first prepared the crystalline *o*-chloromethylphenacyl chloride (I) by the interaction of *o*-chloromethylbenzoyl chloride and diazomethane. The structure of the chloride (I) has been confirmed by analysis, by the close similarity of its infrared spectrum, particularly in the region 2500—1550 cm.$^{-1}$, with that of phenacyl bromide, and by its nuclear magnetic resonance spectrum which shows the presence of two $>CH_2$ groups. The dibromo-analogue of the compound (I) has also been prepared, but is too unstable for synthetic use.



(I)



(II)



(III)

The interaction of the chloride (I) and *p*-toluidine in boiling ethanol containing potassium carbonate gave a highly crystalline compound of molecular formula $C_{23}H_{22}N_2$, which appeared to be the 4-*p*-tolylimino-derivative (II) of the required tetrahydro-4-oxo-2-*p*-tolyl*iso*quinoline; this structure received support from the absence of a =NH band in the infrared spectrum and the presence of a strong band at 1642 cm.$^{-1}$ indicating a conjugated $>C=N-$ group.

The marked stability of this compound, in particular its resistance to acid-hydrolysis and to reduction, did not however accord with structure (II).

We have now prepared the crystalline phenyl and *m*-tolyl analogues of this compound. The phenyl compound is formed slowly by the interaction of the chloride (I) and aniline in cold ethanol, and more rapidly if the solution is boiled, particularly with the addition of potassium carbonate or triethylamine.

The phenyl compound gave a reasonably stable hydrochloride, the infrared spectrum of which indicated a $\equiv NH^+$ group. The base was virtually unaffected by hot dilute hydrochloric or sulphuric acid, by boiling 40% aqueous formaldehyde alone or with hydrochloric acid, and by nitrous acid in cold hydrochloric acid. It gave acetanilide with boiling acetic acid–acetic anhydride, and *N*-phenylphthalimide with sodium dichromate in hot dilute sulphuric acid.

---

[1] Hinton and Mann, preceding paper.

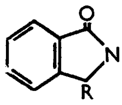
The infrared absorption of the phenyl compound in carbon tetrachloride solution was closely similar to that of the *p*-tolyl analogue in Nujol and in hexachlorobutadiene, and confirmed the absence of an =NH group. The nuclear magnetic resonance spectrum of the phenyl compound in chloroform solution showed two equal resonance peaks at 3·75 and 3·95 chemical shift units, due to the hydrogen atoms in a methyl group interacting with a single adjacent hydrogen atom. There were also four peaks at —0·2, —0·05, 0·12, and 0·27 unit, approximately in the ratio 1 : 3 : 3 : 1, which is the characteristic pattern given by a single hydrogen atom next to a methyl group. This provides strong evidence for the presence of an Me·CH= group, and, combined with the oxidative formation of *N*-phenylphthalimide, indicates that the compound formed by the interaction of the chloride (I) and aniline is 3-methyl-2-phenyl-1-phenylimino*iso*indoline (III; R = Me).

This identification is confirmed by the close similarity of the infrared spectra of authentic 2-phenyl-1-phenylimino*iso*indoline (III; R = H) and our phenyl compound, and of their ultraviolet absorption spectra (and that of the *p*-tolyl compound) in ethanol and in ethanol–hydrochloric acid. Furthermore, condensation of 3-methyl-1-oxo-2-phenyl*iso*indoline (IV; R = Me) and aniline in phosphorus oxychloride gave the 3-phenylimino-compound (III; R = Me) identical with our product.

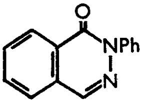
Ultraviolet spectra of the iso*indoline* (III; R = H) *and the "phenyl compound"* (III; R = Me) *in* (A) *ethanolic solution,* (B) *this solution diluted with concentrated hydrochloric acid* (1 *drop*) (λ *in* mμ).

	(A)						(B)			
(III; R = H)	$\lambda_{\text{max.}}$	283	236	$\lambda_{\text{min.}}$	261	220	$\lambda_{\text{max.}}$	246	$\lambda_{\text{min.}}$	229
	ε	10,030	24,400	ε	6720	18,830	ε	15,500	ε	11,140
(III; R = Me)	$\lambda_{\text{max.}}$	282	235	$\lambda_{\text{min.}}$	261	220	$\lambda_{\text{max.}}$	246	$\lambda_{\text{min.}}$	228
	ε	9300	22,900	ε	7570	18,000	ε	16,280	ε	10,720

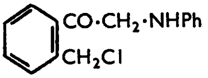
The *iso*indoline (III; R = Me) is of course an amidine, which explains its high stability, particularly towards acid hydrolysis and reduction.



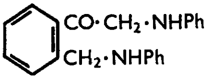
(IV)



(V)



(VI)



(VII)

The formation of the *iso*indoline ring by the action of primary amines on the chloride (I) is surprising: there are many examples of benzene derivatives with two appropriate *ortho*-substituents reacting with amines to give the *iso*indoline ring under conditions which must require either a preliminary tautomeric change of the benzene derivative or a more fundamental molecular rearrangement, but apparently none is known in which a methylene group is extruded as a methyl substituent during the reaction. As examples of the former type, Thiele and Schneider [2] have shown that phthalaldehyde in cold ether reacts with one and two equivalents of aniline to form 1-oxo-2-phenyl*iso*indoline (IV; R = H) and 2-phenyl-1-phenylamino*iso*indoline (III; R = H) respectively. The 1-oxocompound (IV; R = H) is also reported [3] to be formed by the interaction of phthalaldehyde and an excess of aniline at 200—220°, and by the reduction of the compound $C_{14}H_{10}ON_2$, presumably (V), obtained by the interaction of phenylhydrazine and phthalaldehydic acid.[4]

It is known that phenacyl derivatives of aromatic primary amines, Ph·CO·CH_2·NHR, can undergo rearrangement involving an interchange of the phenyl group and a hydrogen atom (or its substituent) of the methylene group,[5] but this reaction is dependent on an

---

[2] Thiele and Schneider, *Annalen*, 1909, **369**, 297.

[3] Hessert, *Ber.*, 1877, **10**, 1445.

[4] Racine, *Annalen*, 1887, **239**, 78.

[5] Brown and Mann, *J.*, 1948, 847, 858; cf. also Crowther, Mann, and Purdie, *J.*, 1943, 58.

acid catalyst, and our condensations have occurred in neutral or mildly alkaline conditions; moreover, the *iso*indoline (III; R = Me) could not be obtained by interaction of the chloride (I) and aniline hydrobromide. The phenacylamine rearrangement, even if it occurred with either of the possible intermediates (VI) and (VII), offers no reasonable mechanism for the formation of *iso*indoline (III; R = Me), and the actual mechanism awaits further investigation.

EXPERIMENTAL

All compounds, unless otherwise stated, were colourless. M. p.s when determined in evacuated tubes are denoted as (E.T.), and temperature of immersion as (T.I.).

The successful preparation of the chloride (I) depends on the rigid adherence to certain conditions specified below: in particular, all apparatus must be carefully dried and closed with drying-tubes during use.

o-*Chloromethylbenzoyl Chloride*.—*o*-Toluoyl chloride, b. p. 212°, was prepared in 94% yield by the interaction of the acid and thionyl chloride.[6] The chloride (48·7 g.), in a weighed flask fitted with an inlet tube and a reflux air-condenser carrying a drying tube, was heated to 170—180° while chlorine was passed through. When the increase in weight indicated 90% monochlorination, the mixture was fractionally distilled, giving *o*-chloromethylbenzoyl chloride (48·6 g., 81%), b. p. 87·5—88·5°/0·5 mm. (lit.,[7] 129—133°/12 mm.). In this fractionation, unchanged *o*-toluoyl chloride can readily be separated; but, if full monochlorination is attempted, the chloromethyl derivative becomes contaminated with the dichloromethyl compound, having almost the same b. p.

A solution of the chloride (6·6 g.) in 98% formic acid [8] (50 c.c.) was shaken at room temperature for 75 min. The addition of water (200 c.c.) then precipitated o-*chloromethylbenzoic acid* (5·8 g., 98%), white plates, m. p. 135—135·5° (Found: C, 56·45; H, 4·3. $C_8H_7O_2Cl$ requires C, 56·3; H, 4·1%).

o-*Chloromethylphenacyl Chloride* (I).—The ethereal diazomethane must be free from ethanol, and it was therefore prepared by the action of aqueous potassium hydroxide on methylnitrosourea, in preference to that of aqueous-ethanolic potassium hydroxide on *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide.

A 2·1% (w/v) solution of diazomethane in ether was thoroughly dried over powdered potassium hydroxide in an ice–salt bath. The solution (330 c.c., 1 mol. of reagent) was filtered rapidly into a nitrogen-filled flask, carrying a dropping-funnel and stirrer, cooled in ice–salt. A solution of triethylamine (16 g., 1 mol.) in ether (20 c.c.) was added to the vigorously stirred solution, followed by *o*-chloromethylbenzoyl chloride (30 g., 1 mol.) in ether (100 c.c.) during 15 min. The stirring was continued for 30 min. and the mixture set aside at room temperature overnight.

The solution was rapidly filtered from triethylamine hydrochloride, and transferred immediately to a 3-necked flask having a thermometer dipping below the surface, and a fine inlet tube reaching to the bottom. The solution was cooled to −2° in ice–salt, and dry hydrogen chloride then passed slowly in, the temperature being kept below 5° meanwhile. The initial precipitate slowly redissolved to give a brown solution, which, when the nitrogen evolution ceased (*ca.* 1½ hr.), was evaporated under reduced pressure at 40°. The residual brown oil was dissolved in methanol (3 × 10 c.c.), and the solution when cooled and stirred deposited the crude chloride (I). Addition of water to the mother-liquor deposited further crops (total, 64%), and recrystallisation from methanol gave the *chloride* (I), colourless needles, m. p. 41—42° (Found: for independent preparations, C, 53·4, 53·3; H, 4·2, 4·1. $C_9H_8OCl_2$ requires C, 53·2; H, 4·0%).

In early experiments, in which 100% monochlorination of the *o*-toluoyl chloride was attempted, the mother-liquors when distilled in steam gave a brown solid which after repeated recrystallisation from aqueous ethanol afforded o-*dichloromethylphenacyl chloride*, needles, m. p. 57·5—58° (Found: C, 45·3; H, 3·0. $C_9H_7OCl_3$ requires C, 45·5; H, 3·0%).

The pure dry chloride (I) can be safely stored for months in a dark refrigerator. It must be handled with care for it is a skin-irritant and a lachrymator.

---

[6] Davies and Perkin, *J.*, 1922, **121**, 2202.
[7] Morgan and Porter, *J.*, 1926, 1256.
[8] Shoesmith, Hetherington, and Slater, *J.*, 1924, **135**, 1312.

o-Bromomethylphenacyl Bromide.—*o*-Bromomethylbenzoyl bromide, white needles, m. p. 36° (lit.,[6] 33—34°), was obtained in 63% yield by the action of bromine on *o*-toluoyl chloride. The reaction with diazomethane was carried out as before, the solution being now treated with hydrogen bromide. The filtered solution was washed in turn with water, 5% aqueous sodium hydrogen carbonate, and water, and finally dried (Na_2SO_4) and cautiously evaporated under reduced pressure. The brown crystalline residue (54%) when recrystallised (charcoal) from methanol, *cyclo*hexane, or light petroleum (b. p. 40—60°) gave the *bromide*, needles, m. p. 55·5—56° (decomp.) (Found: C, 37·3; H, 2·8; Br, 55·5. $C_9H_8OBr_2$ requires C, 37·0; H, 2·8; Br, 54·7%). The bromide decomposed when stored in an evacuated desiccator in the dark for 12 days. Several samples of the crude bromide whilst being dried in a desiccator decomposed violently when almost free from solvent, and the preparation demands safety precautions.

3-*Methyl*-2-*phenyl*-1-*phenylimino*iso*indoline* (III; R = Me).—A mixture of the chloride (I) (2·4 g.), aniline (4 g., 4 mols.), dry potassium carbonate (1·6 g.), and ethanol (20 c.c.) was boiled under reflux for 1 hr., cooled, and poured on ice (200 g.). The crude pale brown iso*indoline* (III; R = Me) (3·2 g., 89%) after several recrystallisations from ethanol gave colourless needles, m. p. 149—151° (E.T.) (Found: C, 84·4; H, 6·2; N, 9·6. $C_{21}H_{18}N_2$ requires C, 84·5; H, 6·1; N, 9·4%).

A solution of the chloride (I) and aniline (2 mols.) in ethanol, when boiled under reflux for 1 hr., cooled, and poured into water, gave a clear solution from which the addition of 10% aqueous sodium hydroxide immediately precipitated the *iso*indoline (III), m. p. 146·5—149° after one recrystallisation from ethanol. Repetition of this experiment with aniline hydrobromide (2 mols.) gave on precipitation a purple oil which could not be obtained solid. A solution of the chloride (I) (0·4 g.) and aniline (1 g., 5 mols.) in ethanol (10 c.c.) was prepared under nitrogen at 0° and set aside overnight at room temperature. The pale brown solution when poured into aqueous sodium carbonate deposited the oily *iso*indoline (III), which when stirred with cold ethanol afforded white crystals, m. p. and mixed m. p. 140—148° (E.T.) without recrystallisation.

Hydrogen chloride, when passed into an acetone–ethanol solution of the *iso*indoline (III), precipitated a brown gum, which when vigorously stirred with ether formed the *hydrochloride* as a white powder, m. p. 205° (darkening from 190°) after drying at 70°/0·1 mm. (Found: C, 75·1; H, 5·5; N, 8·2. $C_{21}H_{18}N_2$,HCl requires C, 75·4; H, 5·7; N, 8·4%).

3-*Methyl*-2-p-*tolyl*-1-p-*tolylimino*iso*indoline* (as III; R = Me).—This compound was prepared by the potassium carbonate method, and the cold dark reaction solution when cautiously diluted with water deposited the crystalline iso*indoline*, m. p. 174—175° (E.T., T.I. 163°) (from ethanol) (Found: C, 84·4; H, 6·9; N, 8·3%; *M*, in boiling acetone, 340, 320, 320. $C_{23}H_{22}N_2$ requires C, 84·6; H, 6·8; N, 8·6%; *M*, 326). It sublimed unchanged at 250°/0·04 mm.

The m-*tolyl analogue*, similarly prepared, formed plates, m. p. 145—155°, from ethanol (Found: C, 84·7; H, 7·1. $C_{23}H_{22}N_2$ requires C, 84·6; H, 6·8%).

Reactions of the Iso*indoline* (III; R = Me).—(1) A suspension of the *iso*indoline (0·2 g.) in an excess of 40% aqueous formaldehyde was boiled under reflux for 3 hr., concentrated hydrochloric acid (0·2 c.c.) being added after 30 min. to hasten dissolution. The cold clear solution when poured into aqueous sodium carbonate deposited the unchanged *iso*indoline, m. p. and mixed m. p. 145—149° (E.T.) after crystallisation from ethanol. The compound was recovered after its solution in ethanol–acetone had been saturated with hydrogen chloride and then boiled for 2 hr.

(2) A solution of the *iso*indoline (0·2 g.) in acetic acid–acetic anhydride (1 : 1 v/v; 5 c.c.) was boiled under reflux for 5 hr., becoming bluish-black. The cold solution, when diluted with water and neutralised with 10% aqueous sodium hydroxide, deposited a black solid, which was collected. The filtrate, on ether-extraction, gave acetanilide. The black solid was apparently unaffected by hot aqueous chromic acid.

(3) A solution of sodium dichromate (2 g.) in water (5 c.c.) was added cautiously to one of the *iso*indoline (0·7 g.) in concentrated sulphuric acid (2 c.c.), with heat evolution. The mixture was heated under reflux for 30 min., cooled, and diluted with water (2—3 c.c.). The *N*-phenylphthalimide which was precipitated formed silky needles, m. p. 204—206°, from ethanol (Found: C, 75·3; H, 4·1; N, 6·0. Calc. for $C_{14}H_{19}O_2N$: C, 75·3; H, 4·1; N, 6·3%). The presence of the phthalimide ring was confirmed by the infrared spectrum.

(4) Bromine water was added dropwise to a solution of the *iso*indoline in dilute hydrobromic acid until a permanent yellow colour developed. Aqueous sodium carbonate precipitated

a *monobromo-derivative*, m. p. 138—140° (E.T.) after several recrystallisations from aqueous ethanol (Found: C, 67·0; H, 4·6; N, 7·6. $C_{21}H_{17}N_2Br$ requires C, 66·9; H, 4·5; N, 7·4%). The position of the bromine atom has not been determined.

The p-*tolyl*iso*indoline* (as III; R = Me) was recovered unchanged after treatment with (*a*) boiling 20% hydrochloric acid for 6 hr., (*b*) sulphuric acid–water (equal vols.) at 100—110° for 1 hr., (*c*) boiling 20% ethanolic potassium hydroxide (w/v) for 4 hr., (*d*) 2 : 4-dinitrobenzaldehyde (1 mol.) in boiling ethanol for 5 hr., (*e*) potassium permanganate in boiling acetone solution for 10 min. A hot ethanolic solution when treated with sodium (6 equivalents), and an acetic acid solution containing platinum oxide when treated with hydrogen at 20°/55 atm. for 17 hr., furnished the unchanged *iso*indoline.

2-*Phenyl*-1-*phenylimino*iso*indoline* (III; R = H).—Preparation of this compound from *o*-chloromethylbenzonitrile has been described.[1] Its preparation from the corresponding 1-oxo*iso*indoline [1] is now described. A mixture of the 1-oxo-derivative (IV; R = H) (10 g.), aniline (20 c.c., 4 mols.), and phosphorus oxychloride (100 c.c.) was boiled under reflux for 3 hr., cooled, and poured into cold water (3 l.). The solution was filtered to remove a large amount of a green solid, which was triturated with water and again filtered. The united extracts were neutralised with 10% aqueous sodium hydroxide, and the precipitated *iso*indoline (III; R = H), when collected and recrystallised from ethanol, had m. p. 151—153° (E.T.) (Found: C, 84·8; H, 6·0; N, 10·1. Calc. for $C_{20}H_{16}N_2$: C, 84·5; H, 5·7; N, 9·9%). The use of phosphorus trichloride in place of the oxychloride left the 1-oxo-derivative unchanged. An ethereal solution of the *iso*indoline (III; R = H) when treated with hydrogen chloride deposited the hydrochloride, m. p. 240° (E.T., darkening from 233°) after drying at 50° (Found: C, 74·7; H, 5·2. Calc. for $C_{20}H_{16}N_2,HCl$: C, 74·9; H, 5·3%).

3-*Methyl*-2-*phenyl*-1-*phenylimino*iso*indoline* (III; R = Me).—Phthalic anhydride was converted into *o*-carboxybenzoylacetic acid,[9] which was selectively decarboxylated to 2-carboxyacetophenone by Rule and Smith's method.[10] Reduction with sodium amalgam then gave 3-methylphthalide.[11]

The crude phthalide (29 g.), aniline (55 g.), and phosphorus oxychloride (100 c.c.) were heated on a steam-bath for 3 hr. The hot mixture was filtered to remove a copious black solid, and the purple filtrate shaken with charcoal to remove much of the colour. The filtered solution when treated with an excess of dilute aqueous sodium hydroxide deposited a flocculent fine brown solid, which was collected with difficulty, dissolved in ethanol, and reprecipitated with water. Recrystallisation from ethanol afforded in small yield the *iso*indoline (III; R = Me), m. p. alone and mixed with that prepared from the chloride (I), 147—148° (Found: N, 9·2. Calc. for $C_{21}H_{18}N_2$: N, 9·4%).

We gratefully acknowledge grants provided by the Department of Scientific and Industrial Research (to I. G. H.) and by the Wellcome Trust (to A. V.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August* 29*th*, 1958.]

---

[9] Gabriel and Neumann, *Ber.*, 1893, **26**, 952.
[10] Rule and Smith, *J.*, 1926, 556.
[11] Gabriel and Michael, *Ber.*, 1887, **10**, 2205; Giebe, *Ber.*, 1896, **29**, 2533.