C. Berti, L. Greci and L. Marchetti*

Istituto Chimico, Facoltà di Ingegneria, Viale Risorgimento, 2, 40136 Bologna, Italy

The synthesis of diindolylmethyl cations by reaction of aldehydes and indoles is described, and their reaction with Grignard reagents, organo-lithium compounds and sodium borohydride, giving the corresponding diindolyl methanes, is reported. The analogous phenyl indolylmethyl cations could never be isolated, but their formation was proved indirectly.

In previous papaer (1,2) we reported on the synthesis and reactivity of cations 1; in this paper we report on the synthesis of the analogous cations 2.

X = Ar   1
= OB₂
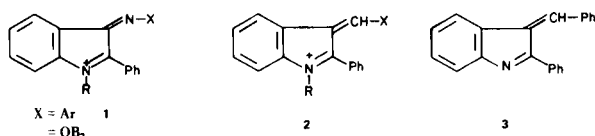
Burr and Gortner (3) claimed in an earlier report that compounds (2, R = H, X = Ph) can be obtained in solution by treatment with sulphuric acid of the corresponding free base 3 formed from the reaction of 2-phenylindole with benzaldehyde. We repeated the Burr and Gortner experiment but we were not able to reproduce their results. This prompted us to reinvestigate the well-known acid-catalyzed reaction between indoles and aldehydes (4), with the specific aim to synthesize compounds 2.

Reactions were carried out at room temperature in the presence of an acid as a catalyst, usually gaseous hydrogen chloride; benzoyl chloride was also used to activate the C=O double bond and it was preferable because easier to dose by analogy with the N=O group activation (1) but, unlike the latter case (1), where cation 4 (X = N) could be isolated, in this case we were not able

X = N
= CH
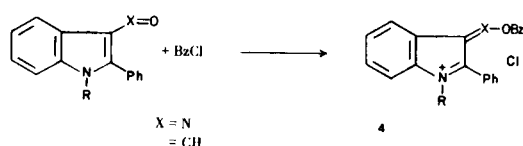
to obtain experimental evidence for the formation of 4 (X = CH).

In Scheme 1 the reaction results are summarized. Reaction 1 gave the bis-indolylphenylmethane 7 as the unique product, whilst reaction 2 afforded to the cation 9 besides to the tris-indolylmethane 10. In this case, the factor that determines the reaction pattern is the solubility of triarylmethane 10. If it is not very soluble in the reaction medium (as for 10b and 10c), it forms and precipitates even when working with an aldehyde/indole molar ratio of 1/1; if, on the contrary, it is soluble (as for 10a), it can only be obtained when an aldehyde/indole molar ratio 1/2 is used, otherwise the reaction stops at the
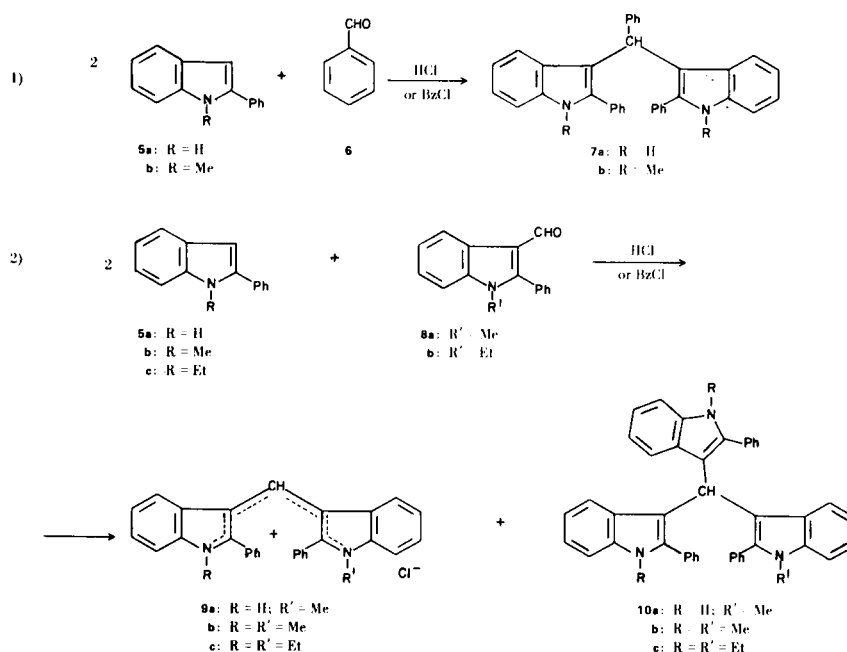
Scheme 1

Table I

Analytical and Spectroscopic Data for Compounds **7, 9** and **10**

Compound	M.p. °C	Yield %	Formula	Found % Calcd. %					Nmr δ
7a	280	80	$C_{35}H_{26}N_2$	C	88.65 88.57	H	5.46 5.52	N 5.85 5.90	6.27 (1H, s, CH); 7.0-7.6 (23H, m, arom.); 8.15 (2H, broad, NH) (a)
7b	220	83	$C_{37}H_{30}N_2$	C	87.99 88.41	H	6.12 6.01	N 5.65 5.57	3.52 (6H, s, CH₃); 5.93 (1H, s, CH); 7.0-7.7 (23H, m, arom.) (a)
9a	272	85	$C_{30}H_{23}ClN_2O_4$	C	70.45 70.65	H	4.60 4.55	N 5.61 5.49	4.22 (3H, s, CH₃); 7.1 (1H, broad, CH); 8.40 (1H, s, NH); 7.3-8.0 (18H, m, arom.) (b)
9b	272	35	$C_{31}H_{25}ClN_2O_4$	C	70.74 71.05	H	4.77 4.80	N 5.81 5.34	4.08 (6H, s, CH₃); 6.9 (1H, broad, CH); 7.3-7.9 (18H, m, arom.) (a)
9c	255	40	$C_{33}H_{29}ClN_2O_4$	C	71.50 71.79	H	5.46 5.29	N 5.29 5.07	1.52 (6H, t, CH₃); 4.47 (4H, q, CH₂); 6.9 (1H, broad, CH); 7.3-7.9 (18H, m, arom.) (a)
10a	305	20	$C_{44}H_{33}N_3$	C	87.22 87.53	H	5.65 5.51	N 7.30 6.96	3.27 (3H, s, CH₃); 6.15 (1H, s, CH); 7.0-7.6 (27H, m, arom.); 7.73 (2H, broad, NH) (c)
10b	335	58	$C_{46}N_{37}N_3$	C	87.70 87.44	H	6.01 5.90	N 6.56 6.65	3.27 (9H, s, CH₃); 6.13 (1H, s, CH); 6.8-7.6 (27H, m, arom.) (c)
10c	235	55	$C_{49}H_{43}N_3$	C	87.56 87.33	H	6.40 6.43	N 6.00 6.23	1.0 (9H, t, CH₃); 3.81 (6H, q, CH₂); 5.90 (1H, s, CH); 6.6-7.6 (27H, m, arom.) (c)

(a) In deuteriochloroform. (b) In perdeuterioacetone. (c) In perdeuteriopyridine.

Table II

Analytical and Spectroscopic Data for Compounds **11, 13** and **14**

| Compound	M.p. °C	Yield %	Formula	Found % Calcd. %					Nmr δ
11a	273	60	$C_{47}H_{39}N_3$	C	86.99 87.43	H	6.24 6.08	N 6.59 6.50	1.02 (3H, t, CH₂CH₃); 3.28 (6H, s, NCH₃); 3.84 (2H, q, CH₂CH₃); 5.98 (1H, s, CH); 6.6-7.6 (27H, m, arom.) (a)
11b	224	63	$C_{48}H_{41}N_3$	C	87.18 87.36	H	6.36 6.26	N 6.32 6.36	1.02 (6H, t, CH₂CH₃); 3.28 (3H, s, NCH₃); 3.84 (4H, q, CH₂CH₃); 5.98 (1H, s, CH); 6.6-7.6 (27H, m, arom.) (a)
13a	162	82	$C_{32}H_{28}N_2$	C	87.15 87.23	H	6.32 6.41	N 6.45 6.36	1.68 (3H, d, CHCH₃); 3.4 (6H, s, NCH₃); 4.65 (1H, q, CHCH₃); 6.8-8.0 (18H, m, arom.) (b)
13b	247	87	$C_{33}H_{30}N_2$	C	87.07 87.18	H	6.65 6.65	N 6.08 6.16	1.18 (3H, t, CHCH₂CH₃); 2.77 (2H, m, CHCH₂CH₃); 3.54 (6H, s, NCH₃); 4.96 (1H, m, CHCH₂CH₃); 7.1-8.35 (18H, m, arom.) (a)
14	191	85	$C_{31}H_{26}N_2$	C	86.82 87.29	H	6.18 6.14	N 7.00 6.75	3.52 (6H, s, NCH₃); 4.28 (2H, s, >CH₂); 6.7-7.6 (18H, m, arom.) (b)

(a) In perdeuteriopyridine. (b) In deuteriochloroform.

stage of cation **9**. The structure assignment for compounds **7, 9** and **10** was based on spectroscopic and analytical data (Table I).

The formation of triarylmethanes **7** and **10** is an acid-catalyzed equilibrium reaction, according to the equation 3. In fact, addition of an acid to a chloroform solution

of **10** causes the immediate appearance of the red colour characteristic for cations **9** and, when perchloric acid is used, the precipitation of the corresponding perchlorates in high yields. Moreover, cations **9** react very rapidly with indoles giving triindolylmethanes **10** in good yields. Finally, another experimental proof of the equilibrium equation

3)

7: Y = Ph
10: Y = 1-R-2-Ph-3-Indolyl

11: Y = Ph
9: Y = 1-R-2-Ph-3-Indolyl
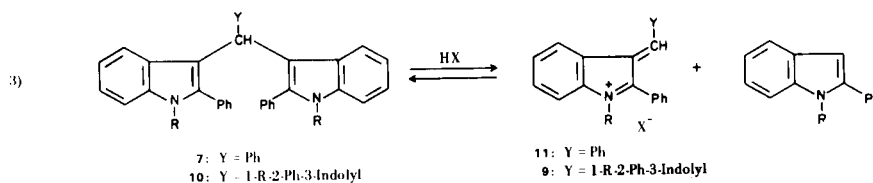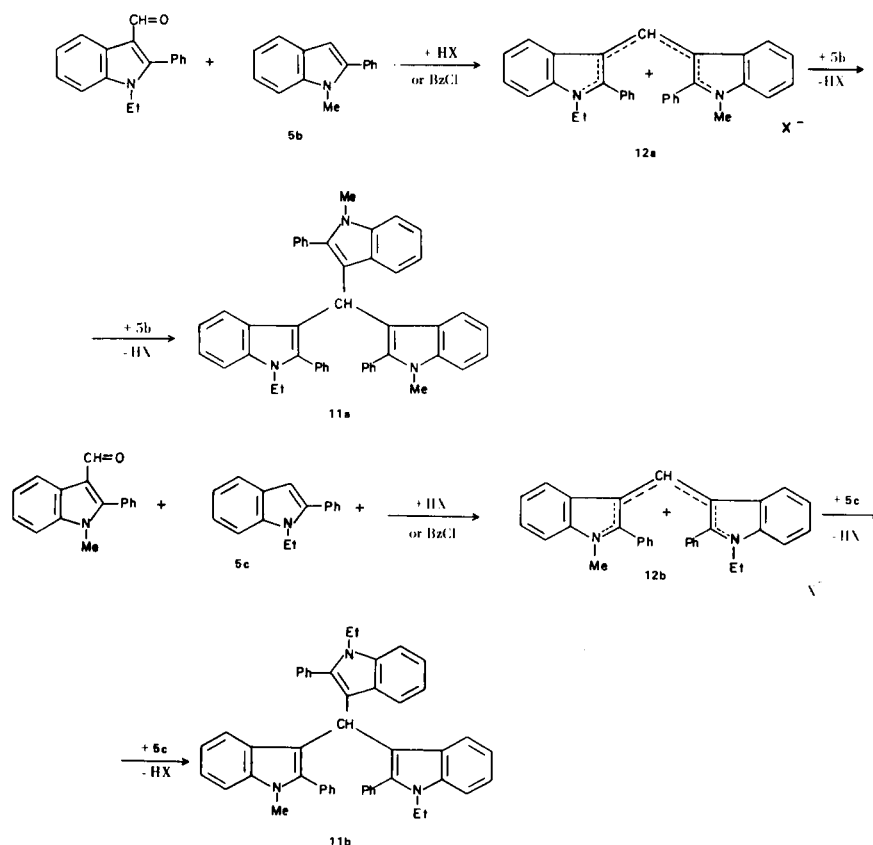
3 can be obtained by considering the reactions of 1-methyl-2-phenylindole with 1-ethyl-2-phenyl-3-indolalde-hyde, and of 1-ethyl-2-phenylindole with 1-methyl-2-phenyl-3-indolaldehyde which yielded the tris-indolyl-methanes **11a** and **11b**, respectively, the structures of which agree with the analytical and nmr data (Table II) and which, as far as could be determined by nmr spectra, were both unique, pure products.

On the other hand, the intermediate cations **12a** and **12b** isolated by the reactions, while having the same m.p. (247°), are not identical and their nmr spectra reveal a different ratio between the areas of the peaks relative to methyl and ethyl groups. This Me/Et ratio is not equal to one, as it should be, but is 1.25 for **12a** and 0.90 for **12b**, which may be explained by arguing that, in the reaction conditions, the tris-indolylmethanes **11a** and **11b** partly cleave, so cations **12** derive in part from the aldehydes and in part from the tris-indolylmethanes **11**. Since, undoubtedly, any one of the three indole rings is just as likely as the other two to detach itself from **11**, whether they be N-methyl or N-ethyl substituted, two N-methyl substituted rings and only one N-ethyl substituted ring being present in **11a**, it may be foreseen that, in the case of **12a**, methyl tends to outweigh ethyl, as is found experimentally. The same holds for **11b**, and explains the average propenderance of ethyl over methyl in **12b**.

In support of this explanation is the fact that a cleavage

performed on pure **11a** and **11b** gave cation mixtures of the **12** variety in which the experimental N-methyl/N-ethyl ratio was 1.55 (starting from **11a**) and 0.62 (starting from **11b**), the theoretical values being 2.0 and 0.5, respectively. The disagreement between the experimental and theoretical values is probably due to product loss during purification and crystallization of the cations prior to the recording of the nmr spectra.

The equilibrium equation 3 is valid also for compounds **7**, but cations **11** are very unstable and could not be isolated; the equilibrium was proved in an indirect way, by allowing **7b** to retrograde in the presence of 2-phenyl-indole, and **7a** retrograde in the presence of 1-methyl-2-phenylindole, respectively. In the first case **7a** and 1-methyl-2-phenylindole and in the second case **7b** and 2-phenylindole could be isolated, respectively, albeit in poor yields (5).

The reason why, unlike cations **9**, cations **11** could never be isolated, can be attributed to the greater stability of **9** in comparison with **11**, owing to the presence of two nitrogen atoms conjugating with the positive centre of the molecule.

As far as the mechanism of the retrogression of triaryl-methanes is concerned, the experimental evidences that an acid catalyst is required and that no diinoldylmethyl cation **9** was obtained in the retrogression of **7**, prompted us to postulate the following reaction pathway:
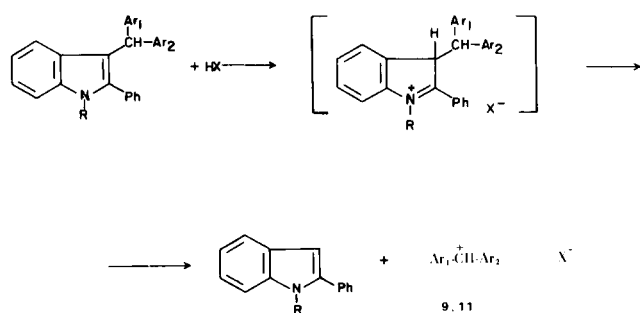
when protonation at C-3 of one indole ring occurs (6).

Cation 9 was reacted with nucleophyles, *i.e.*, Grignard reagents, organolithium compounds and sodium borohydride (7). The experimental results are summarized in Scheme 2.

Scheme 2

13a: R' = Me
b: R' = Et
7b: R' = Ph

14
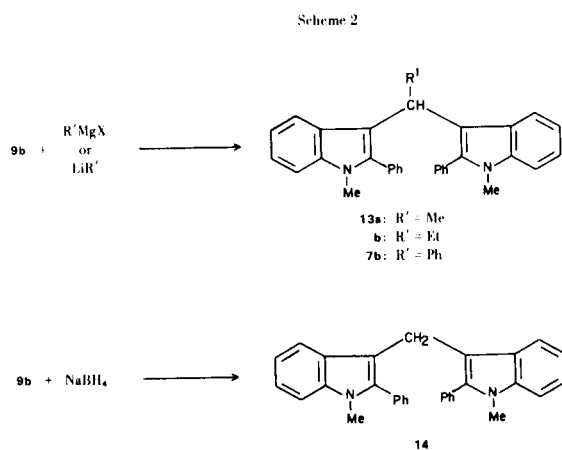
The assigned structures are in agreement with the analytical and spectroscopic data (Table II). In all the reactions studied the nucleophile attacks only the exocyclic carbon atom, unlike the analogous reactions of cations 1, where the nucleophilic attack occurs at the C-2 of the indole ring (1,2).

EXPERIMENTAL

All the melting points were uncorrected. The nmr spectra were recorded with an R 12 B Perkin-Elmer Spectrometer, using deuteriochloroform, perdeuteriopyridine or perdeuterioacetone, with TMS as internal standard; chemical shift values are in δ.

Analytical and spectroscopical data of the compounds 7, 9, 10 are reported in Table I, and compounds 11, 13, 14 in Table II. The benzaldehyde and 2-phenylindole used in this work were pure commercial products. 1-Methyl- and 1-ethyl-2-phenylindole were prepared by Fischer's method, according to Crowther, *et al.* (8). 1-Methyl- and 1-ethyl-2-phenyl-3-formylindole were prepared by Vilsmeier's method, starting from the corresponding indoles, according to Smith (9).

Reaction of 2-Phenylindole and 1-Methyl-2-phenylindole.

Ten mmoles of 2-phenylindole in 70 ml. of chloroform were added under stirring to a solution of 10 mmoles of benzaldehyde and 10 mmoles of benzoyl chloride in 40 ml. of chloroform at room temperature. The solution was allowed to stand at room

temperature for 20 hours, and the precipitate 7a was filtered off and recrystallized from benzene-light petroleum. The filtrate, evaporated to dryness *in vacuo*, gave a solid which when washed with ether, proved to be 7a again. Benzoic acid was isolated from the ethereal solution by extraction with aqueous 10% sodium bicarbonate.

Compound 7b was obtained in the same manner, starting from 1-methyl-2-phenylindole and purifying from ligroin (80-120°). The same results were obtained when the reaction has been catalyzed with gaseous hydrogen chloride.

Reaction of 1-Methyl-2-phenylindole with 1-Methyl-2-phenyl-3-formylindole.

Five mmoles of indole in 25 ml. of acetonitrile was added under stirring to a solution of 5 mmoles of aldehyde and 5 mmoles of benzoyl chloride in 60 ml. of acetonitrile at room temperature. The solution was allowed to stand for 7 hours, then the precipitate 10b was filtered off and recrystallized from pyridine-ligroin (120-140°). One-half g. of sodium perchlorate was added to the filtrate and, after being left to stand for several hours, the sodium chloride precipitated was filtered off. When ethyl ether was added to the new filtrate, compound 9b was isolated and then purified from acetonitrile/ether. Benzoic acid was obtained by extraction of the crystallization solvent of 9b with aqueous sodium bicarbonate and subsequent acidification. The same results were obtained when the reaction was catalyzed with gaseous hydrogen chloride.

Synthesis of 10b from 9b and 1-Methyl-2-phenylindole.

Compound 9b (0.4 g.) and 0.31 g. of 1-methyl-2-phenylindole were dissolved in 30 ml. of acetonitrile at room temperature. The solution was left to stand for 12 hours, and 0.2 g. of 10b were filtered off; with the addition of ethyl ether, 0.15 g. of starting 9b was isolated from the filtrate and excess 1-methyl-2-phenylindole was recovered from the crystallization solvent of 9b.

Reaction of 2-Phenylindole with 1-Methyl-2-phenyl-3-formylindole.

A) Molar Ratio 1:1.

Five mmoles of 2-phenylindole in 20 ml. of acetonitrile were added under stirring to a solution of 5 mmoles of 1-methyl-2-phenyl-3-formylindole and 5 mmoles of benzoyl chloride in 30 ml. of acetonitrile at room temperature. The solution was allowed to stand for 12 hours, no precipitate being formed. Then 1 g. of sodium perchlorate was added and, after a further 3-4 hours at room temperature, the sodium chloride precipitated was filtered off. The diindolyl cation 9a was isolated from the highly concentrated filtrate by the addition of ethyl ether and then purified from ethanol/ethyl ether. Benzoic acid was obtained from the crystallization solvent of 9a in the usual way.

B) Molar Ratio 2:1.

Working as indicated for the preceding reaction, but using an indole/aldehyde molar ratio of 2:1, 0.6 g. of 10a were filtered from the solution after 12 hours and purified from pyridine-ligroin (120-140°). Sodium perchlorate (1 g.) was added to the filtrate and after several hours the precipitated sodium chloride was filtered off. The diindolyl cation 9a (1.2 g.) was isolated from the new filtrate, duly concentrated, by the addition of ethyl ether. Benzoic acid was obtained from the crystallization solvent of 9a in the usual way.

Reaction of 1-Methyl-2-phenylindole with 1-Ethyl-2-phenyl-3-formylindole.

Compound 11a (0.9 g.) (purified from pyridine-ligroin), 0.75 g. of the diindolyl cation 12a (m.p. 247°, purified from aceto-

nitrile/ethyl ether) and benzoic acid were isolated from 5 mmoles of indole, 5 mmoles of aldehyde and 5 mmoles of benzoyl chloride, proceeding as indicated for **10b** and **9b**. The same results were obtained when the reaction was catalyzed with gaseous hydrogen chloride.

Reaction of 1-Ethyl-2-phenylindole with 1-Methyl-2-phenyl-3-formylindole.

Proceeding as indicated for the reaction above and with the same quantities, 0.95 g. of **11b** (purified from pyridine-ligroin), 0.9 g. of the diindolyl cation **12b** (m.p. 247°, purified from acetonitrile-ethyl ether) and benzoic acid were obtained. The same results were obtained when the reaction was catalyzed with gaseous hydrogen chloride.

Cleavage of **11a,b** in the Starting Components with Perchloric Acid.

One ml. of perchloric acid was added to 1 g. of **11a** suspended in 50 ml. of chloroform; **11a** dissolved immediately turning the solution red. Proceeding as indicated for the cleavage of **10b**, the following products were isolated: 0.65 g. of diindolyl cation (which was a mixture of several compounds *N*-substituted with different alkyls, as shown by nmr), and 0.25 g. of a mixture of 1-methyl- and 1-ethyl-2-phenylindole, purified by chromatography on silica, eluting with benzene.

Working with 1 g. of **11b** in the same manner, 0.72 g. of a mixture of diindolyl cations and 0.28 g. of a mixture of indoles were isolated and purified in the same way.

Retrogression of **7b** in the Presence of 2-Phenylindole.

A solution of 0.5 g. of **7b** and 0.19 g. of 2-phenylindole in 30 ml. of chloroform was saturated with gaseous hydrogen chloride and allowed to stand for 20 hours at room temperature; then it was extracted with diluted aqueous sodium bicarbonate and the chloroform layer was separated, dried over sodium sulfate and evaporated to dryness. The residue chromatographed on silica using petroleum ether/ethyl acetate 9:1 gave small quantities of 1-methyl-2-phenylindole and **7a**, identified by comparison with an authentic sample.

Retrogression of **7a** 1-Methyl-2-phenylindole.

Starting from 0.5 g. of **7a** and 0.25 g. of 1-methyl-2-phenylindole, **7b** and 2-phenylindole were isolated in small quantities as described above.

Reaction Between Cation **9b** and Grignard Reagents and Organolithium Compounds.

Two mmoles of Grignard reagent, prepared by the usual method

in THF, was added to 1 mmole of **9b** suspended in 50 ml. of THF. After 1 hour the mixture was poured into 5% aqueous ammonium chloride and extracted with chloroform. The chloroform layer, separated and dried over sodium sulfate, was evaporated to dryness; the residue was chromatographed on silica, using benzene as an eluent. Compounds **13a,b** and **7b** were obtained in over 80% yield: **7b** was identified by comparison with an authentic sample; the analytical and spectroscopic data of **13a,b** (crystallized from benzene/petroleum ether) are listed in Table II. The same results were obtained by using alkyllithium instead of alkylmagnesium halide.

Reduction of **9b** with Sodium Borohydride.

Sodium borohydride (0.3 g.) was added to a solution of 0.5 g. of **9b** with stirring at room temperature. After 30 minutes the mixture was extracted with chloroform and washed with water. The chloroformic layer separated and dried over sodium sulfate, was evaporated to dryness; the residue chromatographed on silica using benzene as an eluent gave 0.3 g. of **14** purified from benzene/petroleum ether: the analytical and spectroscopic data are listed in Table II.

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(5) The intermediate product of the reaction, **7** (R = H, R' = Me) could never be isolated, probably because it was formed in too low yields.

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