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THE "ONE POT" PHOTOCHEMICAL SYNTHESIS OF 2-METHYL-3-CARBOETHOXY-5-PHENYL-INDOLE.

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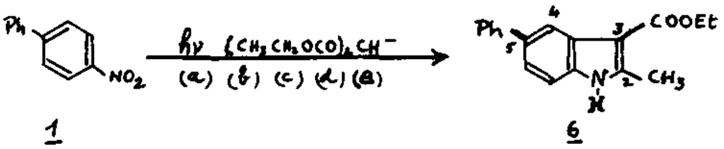
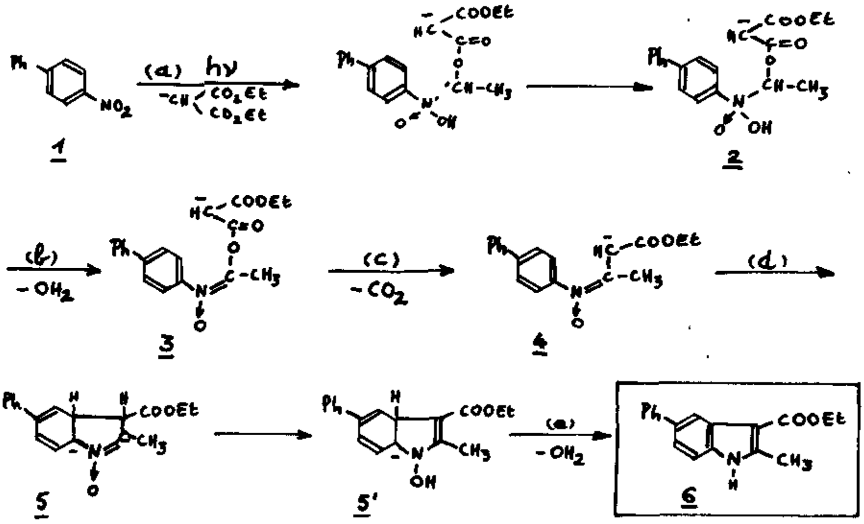
Abstract — *The title compound* 6 is obtained by UV irradiation of 4-nitro-biphenyl in the presence of diethyl malonate anion. The very complex course of the process, involving reactions (a, b, c, d, e) is discussed and a sequence of intermediates 2, 3, 4, 5 is proposed.



a) Intermolecular nitro group reduction with ethyl malonate incorporation (hν) ; b) dehydration ; c) decarboxylation ; d) cyclization ; e) deoxygenation.

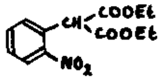
During the course of studies in the field of aromatic nucleophilic photo substitution,[1,2,3,4] in an effort to extend this reaction to other nucleophilic reagents than those generally used[5], we chose a series of malonate anions. We have thus observed a fortuitous and facile synthesis of the title compound 6 which we report here as a rare example of a very complex series of photochemical and thermal reactions.

The photoreduction of nitro aromatic hydrocarbons having a lowest n,π^* excited state is a well documented reaction[6,7] and the incorporation of solvent fragments from ethyl alcohol[8], ethyl ether[9], triethylamine[10] has been reported, but to the best of our knowledge, no mention has ever been made of ethyl malonate incorporation. In the present example, the incorporation of $CH_3CH_2OCOCH_2\text{-}COO\text{-}\dot{C}H\text{-}CH_3$



is indeed the first step of the process leading to 6 because neither methyl malonate nor isopropyl malonate under similar irradiation conditions yield any definite compound homologous to 6.

No photosubstitution took place in the beginning of the process as evidenced i) by the total inertness of t-butyl malonate and malonitrile ii) by the irradiation of two model compounds 7, 8, which would have been obtained if photosubstitution had occurred[11]. The compounds 7 and 8 underwent no intramolecular reaction, thus supporting the intermolecular nitro group reduction, with ethyl malonate incorporation as the first reaction (a) leading to 2.



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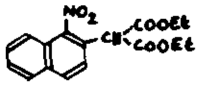

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The nitronic acid 2 looses H_2O (reaction b) a fact already observed by others[6,9] and yields the nitrone 3. A ring closure involving the aromatic ortho carbon atom and the malonate anion (reaction d) has to take place. The driving force for this reaction could be provided by the nitrone function which renders electrophilic the aromatic ortho position[12]. Since, besides the classical Bischler synthesis some other examples of cyclization to the indole skeleton through various mechanisms but starting from the same terminus are known[13,14] we favor an intermediate like 4 (CO_2 extrusion occurring before cyclization).

The deoxygenation of 5 occurs necessarily as the last stop (otherwise there would be no driving force available for cyclization) and the simplest way to explain it is by loss of H_2O following the prototropic shift 5 → 5', although a process related to the photodeoxydation of pyridine N-oxide in ethanol solution[15] could occur.

The moderate chemical yield (18%) of 6 can be explained by i) photoreduction[6,7] of 1 by the ethanolic solvent to give 4-amino biphenyl, always present in variable amounts in the crude mixture of photoproducts ii) the large number of reactions involved. Nevertheless we consider that this "one pot" synthesis of 6 is of interest for practical use and its mechanistic aspects.

Acknowledgements : We acknowledge Prof.R SUNDBERG for helpful suggestions.

EXPERIMENTAL

2-methyl-3-carboethoxy-5-phenyl-indol 6

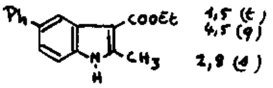
An ethyl ether (90 ml) solution of 4-nitro-biphenyl (0.500 g), added with ethyl malonate (3.2 g) and absolute ethanol (110 ml) containing sodium (0.46 g) is irradiated by a 450 W H.P. mercury lamp (HANOVIA) cooled by a double wall quartz apparatus, with nitrogen bubbling. After 3 h. the solution becomes turbid and the irradiation is stopped. The reaction mixture is poured in water (1 l.) and extracted with ether (3 times). After classical work up, the ethyl malonate in excess is removed under vacuum and the crude reaction mixture (0.450 g) is chromatographed on a column of Alumina (grade II, III). Elution with pentane ; pentane/benzene 90:10, 80:20, 70:30 ; benzene benzene:ether 90:10 ; 80:20 gives mixtures. Final elution with ether gives 6 (144 mg) which was crystallised from acetone-ether mp 179^c (corrected).

Structure elucidation

The compound 6 has a satisfactory elemental analysis ($C_{18}H_{17}NO_2$) and the following spectral data :

- Mass spectrum $M^{+\cdot}$ 279 ; m/e 250 ($M^{+\cdot}$-29), 234 ($M^{+\cdot}$-45) (COOEt) ;
- IR (KBr) cm^{-1} 3280 (NH) ; 1650 (2 or 3-indole-carboxylate) ; λ-UV max (ε) 250 (51.000) 294 (15.500 (Indole skeleton)) ; -NMR (δ) ($CDCl_3$) 1.5, j = 7 Hz (t) 3H ; 4.5 j = 7 (q) 2H ; (COOEt) 2.8 (s) 3H (C=C-CH_3) : 7.2 and 7.9 (slightly resolved signals) 8H, aromatic ; 8.2 exchangeable H (NH).

All the above data are consistent with the proposed structure although the unambiguous assignation to the methyl and carboxylate group is not possible. The comparison between NMR data of 6, 9[16] and 10[17] allows to assign the structure 6 to the photoproduct.



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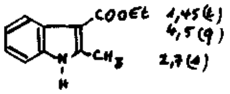

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