CHEMISTRY LETTERS, pp. 511-514, 1981.

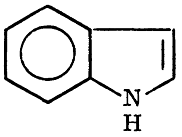
THE FORMATION OF 1- AND 3-SUBSTITUTED INDOLES IN THE REACTION BETWEEN INDOLE AND SODIUM GLYOXYLATE

Francisco AMAT-GUERRI, Roberto MARTINEZ-UTRILLA, and Conrad PASCUAL
Instituto de Química Orgánica General (C.S.I.C.). Juan de la Cierva, 3. Madrid-6, Spain

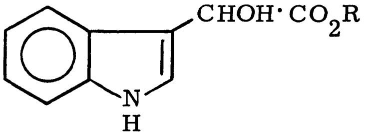
The reaction between indole and sodium glyoxylate under basic conditions produces, in addition to the expected sodium 3-indolylglycolate (3a), the 1-substituted derivative (4a). 3a partially condenses with unreacted indole and with 4a yielding the corresponding 3,3'-diindolylmethane derivatives, 5a and 6a. All compounds were isolated and identified as methyl esters.

Indole derivatives react with aldehydes and ketones yielding condensation products, the structure of which depends on the experimental conditions and the substitution pattern of the reacting indole.[1)] Indolylcarbinols are considered to be intermediates in the formation of the final products in this type of reaction. Although it has not been possible to isolate these indolylcarbinols working in an acidic medium, owing to their known instability, under other conditions it has been possible to stop the reaction at the carbinol stage. The reaction between formaldehyde and indole, in methanol as the solvent and in the presence of sodium methoxide or sodium carbonate, produces 3-indolylmethanol.[2)] Other 3-indolylcarbinols have been isolated in the reaction between indolylmagnesium bromide and pyridine- or isoquinoline-carbaldehyde.[3)] The isolation of dimethyl-1-indolylcarbinol from the reaction between indolylmagnesium iodide and acetone has been reported, although the structure of the compound was not confirmed.[4)] Recently, a 1-indolylcarbinol was obtained from indolylmagnesium bromide and cyclohexanone and its structure was determined.[5)] In contrast to the 3-indolylcarbinols, for which other methods of preparation have been reported,[6)] the 1-indolylcarbinols have not, so far, been synthesized by any other method.

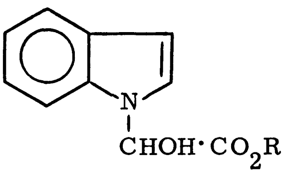
In all the cases mentioned above, the indolylcarbinols were formed in anhydrous media. The reported reaction between indole (1) and sodium glyoxylate (2) in nearly neutral aqueous solution is therefore of interest. This reaction gives sodium 3-indolylglycolate (3a) as the main product and a small amount of the corresponding 3,3'-diindolylmethane derivative (5a) as a by-product.[7)] The latter would be the condensation product normally expected under acidic conditions. This reaction is of interest not only from the synthetic point of view but also in connection with the generation of 3-indolylacetic acid derivatives in Nature, a topic of relevance in the field of plant-growth hormones.[8,9)]



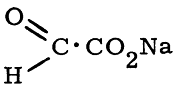
1



3a, b



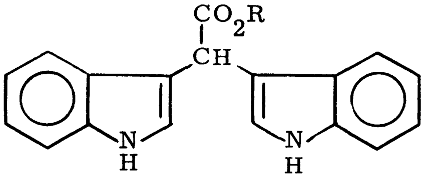
4a, b



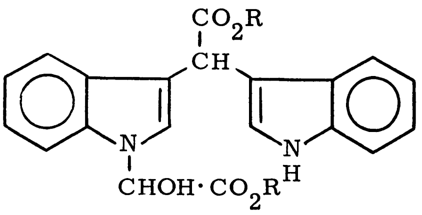
2

a : R = Na

b : R = CH_3



5a, b



6a, b

In looking for an optimum yield of 3a, we reinvestigated the reaction between indole and sodium glyoxylate, particularly the influence of the pH of the medium on the reaction products. In this communication we report the work carried out in order to identify all the products formed in this reaction, which include two 1-indolylcarbinols. Exploratory work on the way in which these products are formed is also presented.

For the sake of convenience, the reaction products were separated and purified as methyl esters. The aqueous solutions were acidified, the products were extracted with ethyl acetate and the crude extract was methylated with diazomethane. In order to exclude the possibility of some of the isolated methyl esters being formed -or their proportions altered- during the extraction or methylation processes, purified sodium 3-indolylglycolate (3a) was previously subjected to the same treatment. Only the methyl ester 3b was obtained.

As reaction media, aqueous alkaline solutions with different pH values -but never higher than 9- were used. In some cases, where methyl esters, instead of the salts, were the reactants, up to 50% methanol was added to increase solubility. Its presence in the medium did not produce any noticeable effect.

Our results show that the pH value of the medium was the predominant factor controlling the course of the reaction and particularly the ratio between the 1- and the 3-substitution products, this ratio increasing as the pH value rose. However, the instability of the carbinols formed -above all 4a- affected the reproducibility of the reaction and made the yields difficult to determine. Consequently, the yields given in Table 1, which also contains the main analytical data of the isolated compounds, are only indicative.

The identification of compounds 3b and 5b as methyl 3-indolylglycolate and methyl 3,3'-diindolylacetate, respectively, offered no particular difficulty.[10] The structure of 3b was confirmed by its synthesis through the reduction of methyl 3-indolylglyoxylate.[11] It is worth mentioning that for 3b, the only one of these compounds already reported in the literature, a melting point of 82.5°C has been given,[11] differing considerably from our value, 50-51°C.

Table 1. Analytical data of the isolated compounds[12)]

Compd	Yield %	m.p. °C	^{1}H-NMR, $CDCl_3$, δ(ppm), 90 MHz				UV, MeOH λ nm (log ε)	IR, KBr $\nu_{C=O}$ cm^{-1}	MS m/z (%)
			CH_3	Ind_2CH	CHOH	H-2			
3b	6	50-51 d	3.67 s	-	5.44 d (J=5 Hz)	7.00 d (J=3 Hz)	273 (3.71) 280 (3.71) 288 (3.63)	1733	205 (30) 146 (100) 144 (16) 118 (68)
4b	30	61-62	3.80 s	-	6.14 s	7.12 d$^{a)}$ (J=3 Hz)	267 (3.71) 278 (3.62) 290 (3.43)	1745	205 (4) 146 (13) 117 (100)
5b	20	45-50 d	3.71 s	5.51 t (J≃0.5 Hz)	-	7.00 d (J=3 Hz)	274 (3.99) 282 (4.01) 291 (3.97)	1725	304 (30) 245 (100) 243 (16)
6b$^{b)}$	35	75-80 d	3.68 s$^{c)}$ 3.71 s 3.72 s	5.47 t 5.48 t (J≃0.5 Hz)	6.00 s (broad)	6.92 m	273 (4.05) 283 (4.07) 291 (3.99)	1740	(see text)

a) H-3: δ 6.55 (d, J = 3Hz). b) A 1:1 mixture of diastereoisomers. c) Relative intensity of the methyl peaks, 1:2:1; in C_6D_6: δ 2.97, 3.00, and 3.26 (1:1:2).

The isolation and purification of 4b, identified as methyl 1-indolylglycolate, were difficult, as heat or acids (including silica) tended to promote its conversion into a mixture of 3b and 1. This transformation was also observable in the variations in its mass spectrum as the source temperature was increased. However, after thorough purification its structure could be determined on the basis of its spectroscopic data. The ^{1}H-NMR spectrum clearly shows the bands corresponding to protons in positions 2 and 3. Furthermore, the N-substitution is reflected in the higher δ-value of the proton in the CHOH group.

Compound 6b gave a mass spectrum identical to that of 5b, suggesting a possible isomer. However, its ^{1}H-NMR spectrum revealed the presence of a CHOH-COOMe group in the molecule, indicating at the same time that 6b was in fact a mixture of diastereoisomers in the ratio 1:1, in accordance with the proposed structure of the 1-hydroxymethoxycarbonylmethyl derivative of 5b. Thermal elimination of methyl glyoxylate easily occurs in this compound, yielding 5b. This happens in the sample introduction system of the mass spectrometer or when the compound is heated in a test tube at 140°C. A similar elimination must be responsible for the above-mentioned conversion of 4b into 1, as it has been suggested in related compounds.[4,5)]

Some comments should be made regarding the formation of the isolated products and the remarkable effect exercised by the pH of the medium on their proportions. As far as 4a is concerned, its formation shows that these derivatives can also be formed in an aqueous alkaline medium and not only when using indolylmagnesium halides. The need for a basic medium in order for this product to be formed suggests that the indole anion may play a determinant role in this reaction. In fact, electrophilic substitution on indoles by alkylating agents can produce 1-substitution. Although this hypothesis is quite attractive, more experimental work is necessary to substantiate it.

As regards the condensation product 5a, there are two possibilities for its formation: a) condensation of two molecules of 3a, with the loss of a molecule of sodium glyoxylate, which would be in accordance with the general behaviour of 3-indolylcarbinols;[1)] and b) nucleophilic attack of 3a by 1, with elimination of water. However, when 3a alone, or its mixture with 1, was subjected to the same experimental conditions used to obtain 3a, it was found that only the mixture 1+3a produced 5a. This condensation also took place when the mixture 1+3b was used, giving the ester 5b directly.

For the formation of the 1-substituted condensation product 6a, two possibilities can also be envisaged: a) the reaction between 2 and 5a; and b) the reaction between 3a and 4a. In order to assess these alternatives, further reactions were carried out. Since the sodium salts 4a and 5a were not easy to isolate, the corresponding esters 4b and 5b were used in these tests. It was found that a mixture of 2 and 5b under the appropriate experimental conditions did not react, while a mixture of 3b and 4b at pH 9 rapidly yielded 6b. These results support the hypothesis b).

REFERENCES AND NOTES

1. R.J.Sundberg, "The Chemistry of Indoles", Academic Press, New York, (1970), p.39.
2. C. Runti, Gazz. Chim. Ital., 81, 613 (1951).
3. H. Bader and W. Oroshnik, J. Am. Chem. Soc., 81, 163 (1959).
4. T. Hoshino, Chem. Ber., 85, 858 (1952).
5. S.H.Zee and K.M.Kuo, J. Chin. Chem. Soc. (Taipei), 24, 57 (1977); C.A., 87, 134920.
6. T.P. Spande, in "Indoles" (W.J. Houlihan, Ed.), John Wiley & Sons, New York, Part III, p. 1 (1979).
7. A. Jones and A.W. Galston, J. Exp. Bot., 20, 257 (1969).
8. a) J.B. Greenberg, A.W. Galston, K.N.F. Shaw, and M.D. Amstrong, Science, 125, 992 (1957); b) V.I.Kefeli, "Natural Plant Growth Inhibitors and Phytohormones", W. Junk b.v. Publishers, The Hague/Boston, (1978), p. 44.
9. Several methyl α-methoxyindolylacetates have been tested as plant growth regulators: W.Reeve, R.S.Hudson, and C.W.Woods, Tetrahedron, 19, 1243 (1963).
10. ^{1}H-NMR spectra of related compounds have been reported: A.Nishinaga, Chem. Letters, 273 (1975) (the methyleter derivative of 3b); ref. 7 (the carboxylic acid corresponding to 5a); see also ref. 5.
11. J.W. Baker, J. Chem. Soc., 458 (1940).
12. Experimental conditions: 500 ml of an aqueous solution of indole (0.01 M) and sodium glyoxylate monohydrate (0.2 M), adjusted to pH 9, were left at room temperature for 24 hr. After acidification (pH 4, HCl), the reaction mixture was extracted with EtOAc and the extract was dried, concentrated and treated cold with CH_2N_2. The mixture of esters so obtained was separated by t.l.c. on silica. Two $CHCl_3$ elutions afforded three fractions, which in decreasing order of Rf value corresponded to 4b, 5b and a mixture of 3b and 6b. The rechromatography of the latter mixture ($CHCl_3$-HOAc, 95:5) yielded 6b (higher Rf value) and 3b. All compounds were further purified by chromatography. 3b can also be recrystallized from benzene.

(Received November 25, 1980)