# HETEROCYCLIC FULGIDES BASED ON 1,2-DIMETHYL-3-FORMYLINDOLE

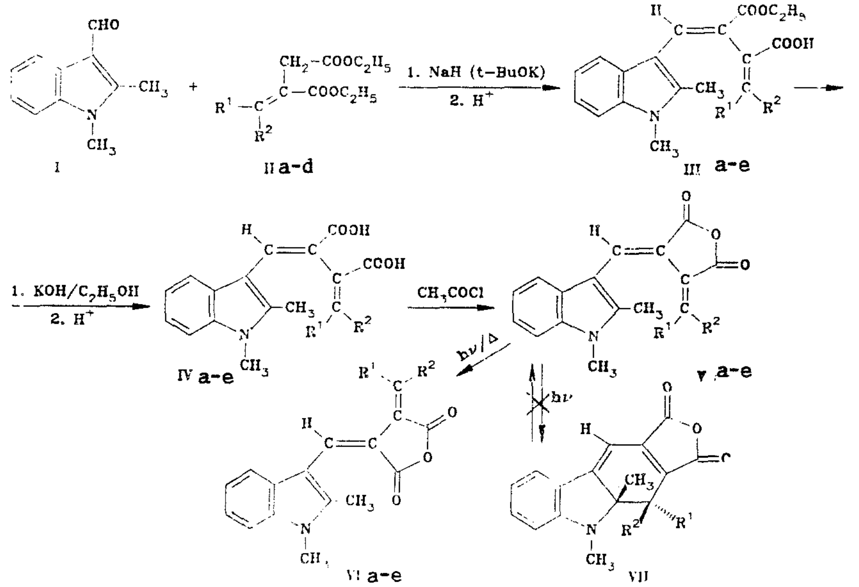
I. Yu. Grishin, Yu. M. Chunaev,
N. M. Przhiyalgovskaya, L. N. Kurkovskaya, and
N. N. Suvorov

UDC 547.462.7'759:541.63:543.422.25

Nonphotochromic fulgides of the indole series, which undergo E, Z isomerization under UV irradiation, were obtained from 1,2-dimethyl-3-formylindole and esters of aryl- and alkylmethylene-substituted itaconic acids by Stobbe condensation in the presence of strong bases.

Fulgides, which are aryl derivatives of bismethylenesuccinic anhydride [1], are currently regarded as a promising class of photochromic compounds [2]. Their photochromism is due to the reverse conrotatory development of a hexatriene system with the formation of polycyclic, more deeply colored compounds [3].

Photochromic heterocyclic fulgides that contain furan, benzofuran, and thiophene fragments are known [4, 5]. In this paper we report the synthesis and properties of fulgides Va-e of the indole series based on 1,2-dimethyl-3-formylindole (I) and diethyl alkyl- and arylmethylene-substituted itaconates II. The need for an N-methyl group in aldehyde I is determined by the conditions used to carry out the Stobbe reaction [6], which lies at the foundation of the synthesis of fulgides and requires the use of strongly basic condensing agents. As regards the second methyl group, it is also needed, since, according to the data in [7], the absence in the aromatic or heteroaromatic ring of a substitutent attached to the carbon atom that participates in the formation of a new ring leads to the rapid loss of photochromic properties as a consequence of the possible 1,5-hydride shift in the photocyclization product.



a $R^1=R^2=CH_3$; b $R^1=CH_3$, $R^2=C_2H_5$; c $R^1=R^2=C_6H_5$; d $R^1+R^2=(CH_2)_5$; e $R^1=$ 1,2-dimethyl-3-indolyl, $R^2=H$

Esters IIa-d were obtained by the method in [8, 9] by the reaction of diethyl succinate with carbonyl compounds.

---

D. I. Mendeleev Moscow Institute of Chemical Technology, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 201-205, February, 1989. Original article submitted June 2, 1987; revision submitted August 3, 1987.

0009-3122/89/2502-0161$12.50 © 1989 Plenum Publishing Corporation

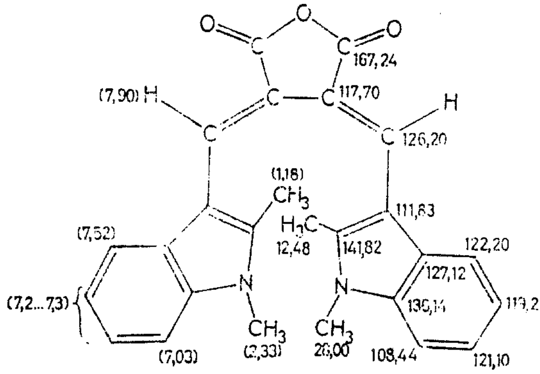


Fig. 1. Data from the $^{13}C$ and (in parentheses) $^1H$ spectra of Ve.

The condensation of 1,2-dimethyl-3-formylindole with II proceeds in a nitrogen atmosphere in the presence of sodium hydride or potassium tert-butozide. Intermediate half esters III (without isolation in the free form) are saponified by an alcohol solution of potassium hydroxide to diacids IV. The latter give fulgides V on heating with acetyl chloride. Diindole fulgide Ve was obtained by direct condensation of 1,2-dimethyl-3-formylindole with diethyl succinate. According to the $^1H$ NMR spectral data (Table 1) the ethylene fragment that contains the heteroring has an E configuration in diacids IVa, b, d and fulgides Va-e. Thus the signal of the vinyl proton is shifted significantly to weak field (7.88-8.06 ppm); this is a consequence of the deshielding effect of the cis-oriented carbonyl group. In IVb and Vb the second ethylene fragment has a Z configuration, as evidenced by the chemical shifts of the methyl group (1.29 and 1.24 ppm, respectively), which are due to the absence of the deshielding effect of the trans-carbonyl group and, on the other hand, to the shielding effect of the closely situated (above or below the methyl group) indole ring [10]. Diindole fulgide Ve has a symmetrical structure; this is confirmed by the coincidence of the signals of the two indole fragments in the $^1H$ and $^{13}C$ NMR spectra (Fig. 1). The positions of the signals of the vinyl protons indicate their cis orientation with respect to the adjacent CO groups, i.e., the E,E configuration of Ve. The stronger-field (than in the case of methyl derivatives of indole [11]) chemical shifts of the $N-CH_3$ and $C-CH_3$ groups (2.33 and 1.18 ppm) observed for this compound are associated with the pronounced noncoplanarity of the Ve molecule; this has also been observed for other fulgides [12].

A comparison of the positions of the long-wave absorption bands of fulgides V and fulgenic acids IV shows that a 70-90 nm bathochromic shift of the long-wave band is characteristic for fulgides.

The photochemical investigations carried out showed that fulgides V, on irradiation with UV light ($\lambda_1$ = 312 nm and $\lambda_2$ = 360 nm) do not form more deeply colored substances VII but undergo only E, Z isomerization with the formation of VI.*

In the case of Va it was shown that E, Z isomerization takes place also when fulgides are heated. Thus E isomer Va, which has a yellow color, is converted to orange Z isomer VI in 55% yield when it is heated to 210°C for 2 min. Isomer VI was isolated by column chromatography. Its $^1H$ NMR spectrum differs substantially from the spectrum of isomer Va. Thus the signal of one of the methyl groups ($R^1$) is observed at much weaker field (2.16 instead of 1.25 ppm for the E isomer); this is explained by its remoteness from the indole ring. The position of the signal of the vinyl proton also changed (7.45 instead of 7.96 ppm), since the deshielding effect of the trans-oriented carbonyl group is absent in the case of the Z isomer. A bathochromic shift of the long-wave absorption band (∿40 nm) is characteristic for the UV spectrum of the Z isomer as a consequence of the more planar geometry of the molecule [13].

Thus the heterocyclic fulgides obtained from 1,2-dimethyl-3-formylindole do not display photochromic properties. At the same time, photochromic fulgides based on 1-methyl-3-formyl- and 1-methyl-3-acetylindole are mentioned in a recently published brief communication [14].

---

*The photochemical behavior of fulgides will be described in detail in a subsequent communication.

TABLE 1. Characteristics of the Fulgenic Acids* and Fulgides

| Compound | Empirical formula | $T_{mp}$, °C | $^1$H NMR spectra, ppm |  |  |  |  | Yield, % ** |
|---|---|---|---|---|---|---|---|---|
|  |  |  | $R^1$ | $R^2$ | N—$CH_3$ | 2-$CH_3$ | HC=C |  |
| IVa | $C_{18}H_{19}NO_4$ | 240...241 | 1,29 | 2,00 | 3,77 | 2,50 | 8,05 | 49 |
| IVb | $C_{19}H_{21}NO_4$ | 235...236 | 1,29 | 2,9*** ($CH_2$); 0,86 t ($CH_3$) | 3,77 | 2,50 | 8,04 | 63 |
| IVd | $C_{21}H_{23}NO_4$ | 240...242 | — | 2,0...3,0*** | 3,78 | 2,50 | 8,06 | 65 |
| Va | $C_{18}H_{17}NO_3$ | 202...204 | 1,25 | 2,12 | 3,76 | 2,49 | 7,96 | 86 |
| Vb | $C_{19}H_{19}NO_3$ | 175...177 | 1,24 | 2,61 q ($CH_2$); 1,16 t ($CH_3$) | 3,78 | 2,51 | 7,97 | 70 |
| Vc | $C_{28}H_{21}NO_3$ | 246...247 | — | 6,2...6,7 | 3,46 | 2,20 | 7,88 | 43 |
| Vd | $C_{21}H_{21}NO_3$ | 201...203 | — | 1,2...1,7 | 3,77 | 2,54 | 7,90 | 66 |
| VIa | $C_{23}H_{17}NO_3$ | 160...162 | 2,16 | 2,32 | 3,73 | 2,41 | 7,45 | 27 |
| Ve | $C_{26}H_{22}N_2O_3$ | 239...241 | — | — | — | — | — | 9 |

---

*The chemical shift of the protons of the carboxy groups of fulgenic acids IV is found at 10.6-11.2 ppm.

**The yields of diacids IV and fulgides Vc, e were calculated on the basis of starting compound I, while the yields of fulgides Va, b, d were based on the corresponding diacids IV.

***The signals are partially overlapped by the signal of the water in the solvent.

The absence of photochromism in the case of Va–e is evidently associated with the steric hindrance created by the methyl group in the 2 position of the indole ring.

## EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The $^1$H and $^{13}$C NMR spectra were obtained with a Bruker 200 SY spectrometer in $(CD_3)_2CO$ for IVa, b, d and in $CDCl_3$ for Va-e and VIa with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at 50 eV. Silica gel (L 40/100) was used for column chromatography. The $R_f$ were determined on Silufol UV-254 plates. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

E-(1,2-Dimethyl-3-indolylmethylene)isopropylidenesuccinic Acid (IVa). A 2.14-g (10 mmole) sample of diethyl isopropylidene-succinate (IIa) [8] and 1.73 g (10 mmole) of 1,2-dimethyl-3-formylindole [15] were added to 1.07 g (40 mmole) of sodium hydride in 70 ml of anhydrous toluene, after which the mixture was stirred at 35°C for 3 h and poured over 80 g of crushed ice. The aqueous layer was separated and acidified with hydrochloric acid (10%). The resulting light-yellow precipitate of monoester IIIa (2.1 g) was hydrolyzed by refluxing for 2 h with an ethanol solution of potassium hydroxide (40 ml, 10%). The solvent was removed by a rotary evaporator, 100 ml of water was added to the residue, the aqueous mixture was filtered, and the filtrate was acidified with hydrochloric acid (10%). The precipitate was removed by filtration, dried, and crystallized from ethanol to give 1.5 g of yellowish crystals of dicarboxylic acid IVa and Rf 0.40 (ether). UV spectrum, $\lambda_{max}$ (log ε): 344 nm (4.2).

E-(1,2-Dimethyl-3-indolylmethylene)-Z-(2-butylidene)succinic Acid (IVb). This compound was similarly obtained from 2.74 g (12 mmole) of diethyl isobutylidenesuccinate (IIb) [8] and 1.73 g (10 mmole) of 1,2-dimethyl-3-formylindole (I) and was crystallized from isopropyl alcohol to give 2.0 g of fine yellowish crystals with $R_f$ 0.38 (ether). UV spectrum, $\lambda_{max}$ (log ε): 347 nm (4.1).

E-(1,2-Dimethyl-3-indolylmethylene)cyclohexylidenesuccinic Acid (IVd). This compound was similarly obtained as in the case of IVa from 3.05 g (12 mmole) of diester IId [8] and 1.73 g (10 mmole) of aldehyde I and was crystallized from isopropyl alcohol to give 2.3 g of yellowish crystals with $R_f$ 0.59 (ether). UV spectrum, $\lambda_{max}$ (log ε): 344 nm (4.1).

E-(1,2-Dimethyl-3-indolylmethylene)isopropylidenesuccinic Anhydride (Va). A 1.5-g (47 mmole) sample of diacid IVa was refluxed with 15 ml (211 mmole) of acetyl chloride for 1.5 h, after which the solvent was removed in vacuo, and the residue was crystallized from ethanol to give 1.2 g of bright-yellow crystals with $R_f$ 0.17 (chloroform). UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 411 nm (4.3).

E-(1,2-Dimethyl-3-indolylmethylene)-Z-(2-butylidene)succinic Anhydride (Vb). This compound was similarly obtained (as in the preceding experiment) from 0.6 g (1.8 mmole) of diacid IVb and 10 ml (141 mmole) of acetyl chloride. Workup gave 0.4 g of bright-yellow crystals with $R_f$ 0.35 (chloroform). UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 417 nm (4.0).

E-(1,2-Dimethyl-3-indolylmethylene)diphenylmethylenesuccinic Anhydride (Vc). A 3.38-g (10 mmole) sample of diethyl diphenylmethylenesuccinate IIc [9] and 1.75 g (10 mmole) of aldehyde I were added to a solution of 0.47 g (12 mmole) of potassium metal in 15 ml (160 mmole) of absolute tert-butyl alcohol, and the mixture was refluxed for 30 min. The tert-butyl alcohol was removed in vacuo, the residue was dissolved in 100 ml of water, the solution was filtered, and the filtrate was acidified to pH 6.5 with hydrochloric acid (10%). The resulting orange oil was extracted with ether, the ether solution was dried with sodium sulfate, and the solvent was evaporated. An alcohol solution of potassium hydroxide (100 ml, 10%) was added to the residue, and the mixture was refluxed for 1 h. The alcohol was removed in vacuo, the residue was dissolved in 70 ml of water, the solution was filtered, and the filtrate was acidified with hydrochloric acid (10%). The resulting yellow precipitate was extracted with ether, the ether solution was dried with sodium sulfate, and the solvent was evaporated to give 0.3 g of diacid IVc, which, by refluxing for 1 h with 20 ml (282 mmole) of acetyl chloride, gave 1.6 g of fulgide Vc. The product was crystallized from ethanol to give red crystals with $R_f$ 0.75 (ether). UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 497 nm (3.7).

E-(1,2-Dimethyl-3-indolylmethylene)cyclohexylidenesuccinic Anhydride (Vd). This compound (0.5 g) was obtained by refluxing 0.80 g (2.3 mmole) of diacid IVd with 10 ml (141 mmole) of acetyl chloride as in the case of Va. The product was crystallized from ethanol to give yellow crystals with $R_f$ 0.36 (chloroform). UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 435 nm (3.8).

E,E-Bis(1,2-dimethyl-3-indolylmethylene)succinic Anhydride (Ve). A 2.8-g (16 mmole) sample of diethyl succinate and 5.2 g (30 mmole) of aldehyde I were added to 1.6 g (60 mmole) of sodium hydride in 80 ml of anhydrous toluene, after which the reaction mixture was stirred for 4 h at room temperature. It was then poured over 100 g of crushed ice, and the aqueous layer was separated and acidified with 5 ml of acetic acid. The resulting precipitate was extracted with ether, the ether solution was dried with sodium sulfate, and the solvent was evaporated. An alcohol solution of potassium hydroxide (40 ml, 10%) was added to the residue, and the mixture was refluxed for 3 h. The alcohol was removed, the residue was dissolved in 100 ml of water, the solution was filtered, and the filtrate was acidified with 5 ml of acetic acid. The resulting precipitate was extracted with ether, the ether solution was dried with sodium sulfate, and the solvent was evaporated to give 4 g of diacid IVe, which was treated immediately with a mixture of 10 ml (106 mmole) of acetic anhydride and 45 ml of ether. The reaction mass was maintained at room temperature for 24 h, after which another 150 ml of ether was added, and the mixture was washed with water. The ether mixture was dried with sodium sulfate, and the ether was removed by distillation in the vacuum created by a water aspirator. The residue was chromatographed in chloroform with a column (4.5 by 60 cm). The fraction that contained fulgide Ve (Rf 0.24) was collected to give 0.6 g of orange crystals. These were then crystallized from ethanol. UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 480 nm (4.1).

Z-(1,2-Dimethyl-3-indolylmethylene)isopropylidenesuccinic Anhydride (VIa). A 0.15-g (0.5 mmole) sample of fulgide Va was heated for 2 min at 210°C, after which the mixture was chromatographed with a column (2 by 55 cm) packed with silica gel by elution with chloroform to give 0.04 g of orange-red crystals of VIa. These crystals were crystallized from ethanol to give a product with $R_f$ 0.61 (chloroform). UV spectrum, $\lambda_{max}$ (log $\varepsilon$): 450 nm (3.6).

## LITERATURE CITED

1. H. Stobbe, Berichte, 3, 3673 (1905).
2. H. G. Heller, Chem. Ind., No. 6, 193 (1978).
3. A. Santiago and R. S. Becker, J. Am. Chem. Soc., 90, 3654 (1968).
4. H. G. Heller, British Patent No. 1464603; Ref. Zh. Khim., 18N275P (1977).
5. A. P. Glaze, S. A. Harris, H. G. Heller, W. Johncock, S. N. Oliver, P. J. Strydom, and J. Whittall, J. Chem. Soc., Perkin 1, No. 5, 957 (1985).
6. H. Stobbe, Ann., 282, 280 (1894).

7. H. G. Heller and M. Szewczyk, J. Chem. Soc., Perkin 1, No. 12, 1487 (1974).
8. C. G. Overberger and C. W. Roberts, J. Am. Chem. Soc., 71, 3618 (1949).
9. H. Stobbe, Berichte, 1, 94 (1897).
10. P. J. Darcy, R. J. Hart, and H. G. Heller, J. Chem. Soc., Perkin 1, No. 6, 571 (1978).
11. S. P. Hiremath and R. S. Hosmane, Adv. Heterocycl. Chem., 15, 277 (1973).
12. M. D. Cohen, H. W. Kaufman, D. Sinnreich, and G. M. J. Schmidt, J. Chem. Soc., B, No. 6, 1035 (1970).
13. H. D. Ilge, H. Langbein, M. Reichenbächer, and R. Paetzold, J. Prakt. Chem., 323, 367 (1981).
14. V. I. Minkin, E. A. Medyantseva, O. G. Lyashik, A. V. Metelitsa, N. M. Andreeva, M. I. Knyazhanskii, and N. V. Volbushko, Khim. Geterotsikl. Soedin., No. 11, 1569 (1986).
15. V. M. Rodionov and T. K. Veselovskaya, Zh. Obshch. Khim., 20, 2202 (1950).

---

# CARBOXYIMIDAZOLES IN THE MANNICH REACTION

N. A. Belyaev and V. S. Mokrushin

UDC 547.784.1.07:781.5.07:
543.422.25'4:542.958.3

Depending on the reagent ratio, 5-dimethylaminomethyl-4-imidazole-4-carboxylic acid and 2,4,5-tris(dimethylaminomethyl)imidazole were obtained in the aminomethylation of imidazole-4-carboxylic and imidazole-4,5-dicarboxylic acids. The oxidation of these compounds with nitric acid leads to imidazole-4,5-dicarboxylic acid.

It is known that imidazole, inasmuch as it is a π-surplus heterocycle, readily undergoes electrophilic substitution reactions [1, p. 55] to give mono-, di-, and trisubstitution products [2]. This is also characteristic for the Mannich reaction. Thus mono- and polysubstituted Mannich bases were obtained from 2-methylimidazole and 4,5-dimethyl- and 2,4-dimethylimidazole in the reaction with formaldehyde and piperidine (or diethylamine), whereas in an acidic medium the reaction of imidazole and 2-methylimidazole led only to N-substituted reaction products [3].

We have studied the behavior in the Mannich reaction of imidazole derivatives that contain carboxy and nitro groups, viz., imidazole-4-carboxylic (I), imidazole-4,5-dicarboxylic (II), and 4-nitroimidazole-5-carboxylic acid and 4-nitroimidazole. It was found that the reaction does not take place at room temperature even in the case of a tenfold excess of the reagents and standing for a long time (72 h). When we heated acid II to 80-100°C with equimolar amounts of dimethylamine and formaldehyde we observed the formation of a mixture of three to four compounds, from which we were able to isolate part of the unchanged starting substance and the principal product, viz., 5-dimethylaminomethyl-imidazole-4-carboxylic acid (III) in the form of hydrochloride IIIa. Under the same conditions, according to TLC data, acid I gives a more complex mixture, one of the components of which is also III. Because of the low chromatographic mobilities, we were unable to isolate individual substances from the mixture.

An increase in the excess amounts of dimethylamine and formaldehyde from sevenfold to tenfold amounts at 80-100°C led to the formation from acids I and II of the same Mannich base, viz., 2,4,5-tris(dimethylaminomethyl)imidazole (IV), which was isolated in the form of mono- and trihydrochlorides IVa and IVb. Compound IVb was also obtained under the same conditions from imidazole.

---

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 206-208, February, 1989. Original article submitted June 10, 1987; revision submitted February 11, 1988.

0009-3122/89/2502-0165$12.50 © 1989 Plenum Publishing Corporation