α-bromononanoyl chloride,[5] α-chlorononanoyl chloride,[3] sorbyl chloride,[6] 2-nonenoyl chloride,[7] 2,4-dichlorophenoxyacetyl chloride,[8] and 2,4,5-trichlorophenoxyacetyl chloride[8] which were prepared in a manner similar to those reported in the literature.

3-Ethyl-2-hexenoyl chloride was prepared from the corresponding acid and $SOCl_2$ by a procedure employed for the preparation of similar acid chlorides;[7] bp 72–74° (12 mm), yield 84%. This material was characterized by conversion to **27**.

Anilides and Complexes. Method A.—A solution of the substituted aniline (0.05 mole) and a drop of H_2SO_4 in 15–18 ml of the acid anhydride was refluxed for 2–3 hr, cooled, and poured into water. The anilide was collected, washed with water, and recrystallized.

Method B.—The acid chloride (0.055 mole) was added slowly to a stirred and refluxed solution of the aniline (0.050 mole) in 150–200 ml of toluene, methylcyclohexane, or a mixture of these solvents. Reflux was continued until HCl evolution ceased. The solution was cooled to allow crystallization or, in some cases, the solvent was evaporated and the anilide was recrystallized.

Method C.—The acid chloride (0.05 mole) was added dropwise to a stirred solution of the aniline and triethylamine (0.05 mole of each) in 200–300 ml of ether. The mixture was refluxed for 2–4 hr, cooled, and filtered to remove triethylamine hydrochloride. The solvent was evaporated and the anilide was recrystallized using activated carbon. In those instances [**6** (**40**), **11** (**43**), **13** (**44**), and **14** (**45**)] in which a complex formed between the 4-nitro-3-trifluoromethylaniline and the corresponding anilide, the complexes were broken up by dissolving the complex in ether and adding an excess of ethereal HCl. The precipitated aniline hydrochloride was separated and the filtrate was evaporated to yield the anilide. The aniline hydrochloride readily lost HCl and reverted to the aniline. No reaction occurred between the complexes and dilute HCl.

Method D.—Bromine (0.014 mole) in 25 ml of CCl_4 was added dropwise at 0° to a stirred mixture of 0.014 mole of the unsaturated anilide (**26**) in 100 ml of CCl_4 and stirred at 0–5° for 6 hr and at reflux for 0.5 hr. The solvent was evaporated and the residue was recrystallized.

Method E.—A solution of 0.003 mole of **24** and 0.006 mole of potassium acetate in 50 ml of ethanol was refluxed for 2 hr. The mixture was cooled and filtered, and the filtrate was evaporated. An ether solution of the oily residue was washed with water, dried, and evaporated.

Method F.—The salt of the anilide was prepared by refluxing for 2 hr equimolar quantities (0.014 mole) of the anilide (**14**) and sodium in 50 ml of dry toluene. Dimethyl sulfate (0.007 mole) was added. The solution was refluxed for 2 hr, washed with water, dried, treated with activated carbon, and evaporated.

Method G.—Equimolar quantities (0.003 mole) of 4-nitro-3-trifluoromethylaniline and the 4-nitro-3-trifluoromethylanilide were dissolved in 35 ml of a 1:1 mixture of methylcyclohexane and toluene. Upon cooling, the complex precipitated and was purified by recrystallization.

Infrared Spectra.—The infrared spectra of the solid anilides and complexes were taken as Nujol mulls using a Beckman IR-5 spectrophotometer. The liquid samples were measured as thin layers between salt plates.

Bacteriostatic Test Procedure.—The standard procedure used in screening the compounds against *S. aureus* (ATCC No. 6538) was as follows. Stock solutions were prepared by dissolving 100 mg of the test compound in 10 ml of acetone, alcohol, or other solvent. The stock solutions were diluted serially by pipetting 2 ml of the stock solutions into 18 ml of sterile nutrient agar to obtain a 1×10^3 dilution and continuing in the same manner for dilutions up to 1×10^6. The agar was poured into Petri dishes, allowed to harden, and spot inoculated with one drop of a cell suspension of *S. aureus* which was prepared by suspending the growth from a 24-hr nutrient agar slant culture in 10 ml of distilled water. The plates were incubated at 37° for 48 hr and examined for the presence or absence of growth. The results reported are the minimum concentration of the test compound which will completely inhibit the growth of the bacteria.

(5) A. Hopwood and C. Weizmann, *J. Chem. Soc.*, 1577 (1911).
(6) H. Staudinger and H. Schneider, *Ber.*, **56**, 699 (1923).
(7) E. Ott and K. Zimmermann, *Ann.*, **425**, 314 (1921).
(8) J. W. Wood and T. D. Fontaine, *J. Org. Chem.*, **17**, 891 (1952).

Acknowledgment.—We wish to thank Mr. K. L. Godfrey for consultation and advice during the course of the investigation, Mr. P. D. McDonald for the microbiological evaluations, Dr. Bernard Katlafsky for assistance in spectral interpretation, and Messrs. John L. O'Sullivan and Ottmar S. Kring for part of the analytical data.

The Mitomycin Antibiotics. Synthetic Studies. XIX.[1] Synthesis of Indoloquinone Analogs with Certain C-3 Variants

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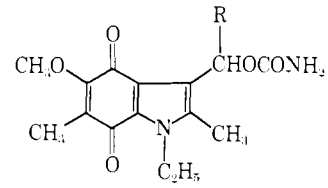
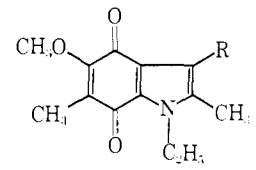
As part of our program for the preparation of analogs of indoloquinones (*e.g.*, Ia)[2] related to the mitomycin antibiotics, it was of interest to ascertain those structural features at C-3 consistent with biological activity. In this paper we report the preparation of analogs of Ia wherein the 3-carbamoyloxymethyl group is substituted with an α-methyl group or is replaced by hydrogen, methyl, or certain substituted methyl functions.

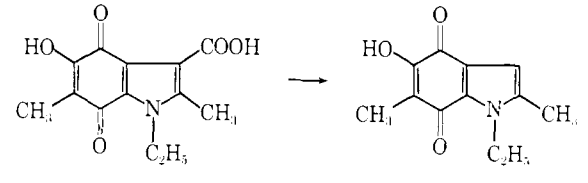


Ia, R = H
Ib, R = CH_3



IIa, R = H
IIb, R = CH_3

The 3-hydrogen analog IIa was obtained by acid-catalyzed decarboxylation of the known quinone acid III.[2b] Methylation of the resulting IV to the desired methoxyquinone IIa was effected with methyl sulfate and potassium carbonate in acetone. A similar methylation of 1-ethyl-5-hydroxy-2,3,6-trimethylindole-4,7-dione[2b] gave the 3-methyl analog IIb.

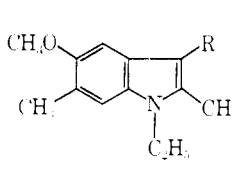


III IV

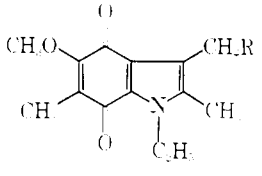
For the preparation of the α-methyl homolog Ib, 1-ethyl-2,6-dimethyl-5-methoxyindole (V)[2] was converted to the 3-acetyl derivative VI with acetic anhydride and sodium acetate.[3] This ketone was then converted into Ib using the procedures previously described for the transformation of the corresponding 3-formyl derivative VII into Ia.[2b] With respect to the homolog

(1) Paper XVIII: G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 23 (1967).
(2) (a) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem Soc.*, **86**, 3878 (1964); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.* **10**, 1 (1967).
(3) A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **26**, 1449 (1956); *Chem. Abstr.*, **50**, 14710*i* (1956).

Ib, which was obtained as an orange oil, we would note that the limited amount of material precluded the usual combustion analyses; however, the spectral properties of this material served to define it as Ib.



V, R = H
VI, R = $COCH_3$
VII, R = CHO



VIII, R = OH
IX, R = Cl
X, R = $SCOCH_3$
XI, R = $OCOOC_6H_5$
XII, R = OCH_3

Recent biochemical evidence suggests that alkylation may play an important role in the mechanism by which the mitomycins exert their biological effect.[4] One probable alkylation site is the substituted 3-methyl group with the carbamoyloxy function serving as the leaving group.[4] Therefore, it was particularly pertinent to prepare analogs in which the carbamoyloxy group was replaced by other potential leaving groups.[5] Thus, treatment of alcohol VIII[2] with thionyl chloride gave the 3-chloromethyl derivative IX, which with potassium thioacetate furnished thiol ester X. Methanolysis of phenylcarbonate XI[2] gave the 3-methoxymethyl analog XII; similar treatment of the free alcohol VIII was ineffective.[6]

Biology.—With the exception of the α-methyl homolog Ib, the various analogs were inactive when assayed *in vitro* at 100 μg/ml against representative bacteria by the agar dilution technique.[7] The activity of Ib is less than that of the 3-hydroxymethyl carbamate Ia. The former compound inhibits the growth of *Staphylococcus aureus* var. Smith, *Staphylococcus aureus*, 69, and *Streptococcus pyogenes*, C203, at 50 μg/ml.

Experimental Section

General.—Melting points were determined in an open capillary tube on a Mel-Temp apparatus and are corrected. The petroleum ether used was that fraction boiling at 30–60° unless specified otherwise. Ultraviolet spectra were determined in methanol solution using a Cary recording spectrophotometer, and the infrared spectra were determined in pressed KBr disks with a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal standard; $CDCl_3$ was used as the solvent except where noted otherwise; in the description of these spectra, the signals are expressed as *x*s (singlet), *x*d (doublet), *x*t (triplet), or *x*q (quartet), where *x* indicates the number of protons indicated by integration. All evaporations were carried out at reduced pressure.

1-Ethyl-5-hydroxy-2,6-dimethylindole-4,7-dione (IV).—A suspension of 600 mg (2.28 mmoles) of 1-ethyl-5-hydroxy-2,6-dimethyl-4,7-dioxoindole-3-carboxylic acid (V)[2b] in 100 ml of concentrated HCl was heated at reflux for 40 min. The reaction mixture was cooled to give 372 mg (74%) of red solid, mp 266–268°. Recrystallization from CH_2Cl_2–petroleum ether gave red crystals: mp 266–268°; λ_{max} 228, 298, 365, 510 mμ (ϵ 19,900, 17,300, 2980, 1630); λ 2.98, 6.06, 6.12 μ.

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.84; H, 5.62; N, 6.68.

1-Ethyl-5-methoxy-2,6-dimethylindole-4,7-dione (IIa). A stirred mixture of 331 mg (1.51 mmoles) of IV, 3.31 g of K_2CO_3, and 6.5 ml of methyl sulfate in 165 ml of acetone was heated at reflux temperature for 45 min, whereafter stirring was continued at room temperature for 2 hr. The mixture was filtered, and the residue was washed well with acetone. The combined filtrate and washings were evaporated, the excess dimethyl sulfate being removed at oil-pump pressure. The residue was dissolved in acetone and diluted with water to furnish 278 mg of solid, mp 187–190°. Recrystallization from CH_2Cl_2–petroleum ether gave crystals: mp 187–190°; λ_{max} 222, 287, 370, 500 mμ (ϵ 18,000, 13,120, 2320, 2440); λ 6.0, 6.09, 6.17, 10.04 μ.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.67; H, 6.38; N, 6.14.

1-Ethyl-5-methoxy-2,3,6-trimethylindole-4,7-dione (IIb). 1-Ethyl-5-hydroxy-2,3,6-trimethylindole-4,7-dione[2b] (146 mg, 0.63 mmoles) was methylated with methyl sulfate as described in the preparation of IIa. The crude product was chromatographed on Florisil (magnesia–silica gel); the material eluted by CH_2Cl_2 was recrystallized from petroleum ether to give 74 mg of red crystals: mp 90.5–91.5°; λ_{max} 233, 287, 360, 460 mμ (ϵ 15,300, 13,800, 3080, 1700); λ 6.01; 6.08, 6.20, 6.53, 6.75 μ; pmr, 79 Cs, J = 7.5 cps, $NCH_2(CH_3)$, 117 Cs, 6-CH_3, 131, 135 Cs each, 2- and 3-CH_3, 239.5 Cs, OCH_3, 261 cps (2q, J = 7.5 cps, NCH_2CH_3).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.51; H, 6.94; N, 6.03.

3-Acetyl-1-ethyl-5-methoxy-2,6-dimethylindole (VI).—A stirred mixture of 12.9 g (0.064 mole) of 1-ethyl-5-methoxy-2,6-dimethylindole (V)[2] and 10 g of sodium acetate in 300 ml of acetic anhydride was heated at reflux temperature for 6 hr. The reaction mixture was cooled, poured onto crushed ice, and stirred for 3 hr, whereafter it was warmed on the steam bath and then stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2, and the extract was washed successively with water, saturated $NaHCO_3$ solution, and finally with water. The dried organic solution was taken to dryness to give 14 g (89%) of an oil. A sample of this oil was distilled, and the fraction with bp 150–170° (0.2 mm) was crystallized from petroleum ether to give a white solid: mp 88–90°; λ_{max} 218, 255, 282, 308 mμ (ϵ 28,800, 16,300, 12,100, 14,700); λ 6.11 μ.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 73.44; H, 7.81; N, 5.71. Found: C, 72.82; H, 7.79; N, 5.65.

3-Acetyl-1-ethyl-5-hydroxy-2,6-dimethylindole.—A mixture of 12 g of crude VI and 13.1 g of $AlCl_3$ in 450 ml of xylene was stirred at reflux temperature for 5 hr. The cooled mixture was treated with cracked ice and digested to give 8.2 g (75%) of pink solid, mp 250–255°. A sample was recrystallized from acetone to give cream-colored crystals: mp 262–265° dec; λ_{max} 218, 258, 284, 312 mμ (ϵ 26,500, 13,400, 9920, 12,700); λ 3.16, 6.32, 9.15, 10.15 μ.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.19; H, 7.41; N, 6.32.

3-Acetyl-1-ethyl-2,6-dimethylindole-4,5-dione.—To a stirred solution of 2.05 g (7.65 mmoles) of potassium nitrosodisulfonate in 153 ml of 0.167 *M* KH_2PO_4 solution and 300 ml of water was added a solution of 295 mg (1.28 mmoles) of 3-acetyl-1-ethyl-5-hydroxy-2,6-dimethylindole in 300 ml of hot acetone. The blue solution turned brown on addition of the indole and became purple within 30 min. The resulting mixture was stirred at room temperature for 4 hr. The solution was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saline, concentrated to a small volume, and filtered. The filtrate was evaporated on the steam bath with concomitant addition of petroleum ether until crystallization began. The mixture was cooled to give 176 mg of dark brown solid, mp 162–165°. Recrystallization from CH_2Cl_2–petroleum ether gave dark brown needles: mp 164–166°; λ_{max} 232, 262 (sh), 346, 515 mμ (ϵ 26,500, 7840, 3000, 1590); λ 6.01 μ.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.98; H, 6.27; N, 5.78.

3-Acetyl-1-ethyl-5-hydroxy-2,6-dimethylindole-4,7-dione.—To a stirred mixture of 657 mg (2.68 mmoles) of 3-acetyl-1-ethyl-2,6-dimethylindole-4,5-dione in 8 ml of acetic anhydride was added 0.2 ml of boron trifluoride etherate. The solid dissolved

(4) (a) V. N. Iyer and W. Szybalski, *Science*, **145**, 55 (1964); (b) A. Weissbach and A. Lisio, *Biochemistry*, **4**, 196 (1965).

(5) The preparation of analogs with acyloxymethyl groups or N-substituted carbamoyloxymethyl at C-3 will be reported separately.

(6) Contrast the behavior of 2-phenyl-3-indolylmethanol: E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

(7) For a complete description of this test procedure as conducted by Mr. A. C. Dornbush in these laboratories see G. R. Allen, Jr., B. R. Baker, A. C. Dornbush, J. P. Joseph, H. M. Kissman, and M. J. Weiss, *J. Med. Pharm. Chem.*, **2**, 391 (1960).

and the purple mixture became dark brown. The reaction was stirred at room temperature for several hours. Cracked ice was added, and the mixture was stirred until the excess acetic anhydride hydrolyzed. The resulting solid was collected by filtration and washed with water to give 888 mg of a brown solid. This solid was washed with cold methanol to give 467 mg of a yellow solid, mp 195–200°. This material was used in the next step without further purification.

A stirred mixture of 2.053 g (5 mmoles) of the above solid in 107 ml of water and 15.7 ml of 25% NaOH was heated at reflux under nitrogen until solution occurred. The solution was filtered and a stream of air was introduced into the filtrate for 40 min. The resulting purple solution was acidified by addition of HCl. The resulting orange solution was extracted with CH_2Cl_2 and the extracts were washed with water. The dried extracts were evaporated, and the residue was recrystallized from CH_2Cl_2–petroleum ether to give 410 mg (33%) of red crytals: mp 172–175°; λ_{max} 227, 298, 338 mμ (ε 19,050, 13,700, 4950); λ 3.01, 5.99, 6.05, 6.21, 8.9 μ.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 63.08; H, 5.58; N, 5.43.

3-Acetyl-1-ethyl-5-methoxy-2,6-dimethylindole-4,7-dione.—3-Acetyl-1-ethyl-5-hydroxy-2,6-dimethylindole-4,7-dione (163 mg, 0.625 mmole) was alkylated with 4 ml of methyl sulfate in the presence of 1.6 mg of K_2CO_3 as described for IIa. The product (91 mg, 53%) was obtained from CH_2Cl_2–petroleum ether as orange crystals: mp 126–127°; λ_{max} 222, 286, 338 mμ (ε 20,200, 11,400, 3990); λ 5.95, 6.01, 6.07, 6.17, 8.98 μ; pmr, 80 (3t, J = 7.0 cps, CH_2CH_3), 118 (3s, 6-CH_3), 144 (3s, $COCH_3$), 159 (3s, 2-CH_3), 241 (3s, CH_3O), 265 cps (2q, J = 7.0 cps CH_2CH_3).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.77; H, 6.51; N, 5.35.

1-Ethyl-3-(1-hydroxyethyl)-5-methoxy-2,6-dimethylindole-4,7-dione.—A stirred solution of 100 mg (0.3 mmole) of 3-acetyl-1-ethyl-5-methoxy-2,6-dimethylindole-4,7-dione in 10 ml of methanol was heated to reflux and 100 mg of $NaBH_4$ was added under nitrogen. The resulting mixture was heated for 1–2 min and then allowed to stir for 1 hr at room temperature. To the solution was added 1 ml of acetone, and after 5 min 1 ml of 1 N $FeCl_3$ in 0.1 N HCl solution. The resulting mixture was distributed between CH_2Cl_2 and water. The organic phase was washed with saline, dried, and evaporated to give a reddish oil having λ_{max}^{MeOH} 230, 287, 358 mμ, and λ_{max}^{KBr} 2.90, 6.05, 6.16, 6.20, 9.10, 10.00 μ. This oil was used in the next step without further purification.

1-Ethyl-3-(1-hydroxyethyl)-5-methoxy-2,6-dimethylindole-4,7-dione Phenylcarbonate.—To an ice-chilled, stirred solution of 300 mg (1.08 mmoles) of crude 1-ethyl-3-(1-hydroxyethyl)-5-methoxy-2,6-dimethylindole-4,7-dione in 6 ml of pyridine was added 0.3 ml of phenyl chloroformate. The resulting mixture was stirred and warmed intermittently on the steam bath over a 3-hr period. The mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with saline, dried, and evaporated to give 290 mg of an orange oil which was used for the subsequent step without purification.

1-Ethyl-3-(1-hydroxyethyl)-5-methoxy-2,6-dimethylindole-4,7-dione Carbamate (Ib).—Ammonia gas was introduced into a solution of 90 mg of crude 1-ethyl-3-(1-hydroxyethyl)-5-methoxy-2,6-dimethylindole-4,7-dione phenylcarbonate in 20 ml of ether, chilled in a Dry Ice bath, until an equal volume of NH_3 had condensed. The Dry Ice bath was removed, and reaction was allowed to stand under a Dry Ice condenser for 4 hr. The excess NH_3 was allowed to evaporate, and the reaction was diluted with ether, washed with saline, dried, and evaporated to give an orange oil. The oil was chromatographed on Celite (diatomaceous silica) using a heptane–ethyl acetate–methanol–water (70:30:17:4) system;[8] the fraction with peak hold-back volume 2.94 (V_m/V_s = 2.34) was evaporated to give 15 mg of an orange oil: λ_{max} 232, 285, 348, 460 mμ (ε 14,350, 11,650, 2720, 1120); λ_{max} 2.82, 2.9, 5.77, 5.99, 6.06 μ; pmr, 79 (3t, J = 7.5 cps, CH_2CH_3), 94 (3d, J = 7.0 cps, CH_3CHO), 116 (3s, 6-CH_3), 141 (3s, 2-CH_3), 239 (3s, CH_3O), 259 (2q, J = 7.5 cps, CH_2CH_3), 294 (2 broad, NH_2), 373 cps (1 q, J = 7.0 cps, CH_3CHO).

3-Chloromethyl-1-ethyl-5-methoxy-2,6-dimethylindole-4,7-dione (IX).—A solution of 100 mg (0.38 mmole) of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione (VIII)[2] and 5 ml of $SOCl_2$ was stirred at room temperature for 40 min. The excess $SOCl_2$ was evaporated, and the product was isolated with CH_2Cl_2. The residue was recrystallized from ether–petroleum ether to give 75 mg (70%) of yellow crystals: mp 141–142°; λ_{max} 232, 285, 348, 455 mμ (ε 17,050, 14,050, 5630, 1270); λ 6.03, 6.09, 6.2 μ.

Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 59.79; H, 5.87; N, 4.45; Cl, 12.56.

3-Acetylthiomethyl-1-ethyl-5-methoxy-2,6-dimethylindole-4,7-dione (X).—A solution of 50 mg (0.17 mmole) of 3-chloromethyl-1-ethyl-5-methoxy-2,6-dimethylindole-4,7-dione (IX) and 20.3 mg (0.17 mmole) of potassium thioacetate in 10 ml of acetone was stirred at room temperature for 1 hr. The solution was diluted with water to give 46.7 mg (81%) of solid, mp 109–111°. A sample recrystallized from CH_2Cl_2–petroleum ether had mp 111–112°; λ_{max} 230, 286, 355, 465 mμ (ε 21,000, 13,650, 3210, 1670); λ 5.95, 6.10, 6.25 μ.

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.80; H, 5.96; N, 4.36; S, 9.97. Found: C, 59.47; H, 6.12; N, 4.28; S, 9.87.

1-Ethyl-5-methoxy-3-methoxymethyl-2,6-dimethylindole-4,7-dione (XII).—A solution of 100 mg (0.38 mmole) of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethylindole-4,7-dione phenylcarbonate (XI)[2] in 10 ml of methanol was heated on the steam bath for 10 min. The solvent was evaporated, and the residue was recrystallized from dilute methanol to give red crystals: mp 90–91°; λ_{max} 231, 285, 345, 462 mμ (ε 15,900, 12,700, 3040, 1105); λ 6.01, 6.13, 6.25, 9.02, 9.24 μ; pmr, 79.5 (3t, J = 7.0 cps, CH_2CH_3), 117 (3s, 6-CH_3), 137.5 (3s, 2-CH_3), 204 (3s, CH_2OCH_3), 239.5 (3s, 5-CH_3O), 260 (2q, J = 7.0 cps, CH_2CH_3), 276 cps (2s, CH_2OCH_3).

Anal. Calcd for $C_{15}H_{19}NO_4$. C, 64.96; H, 6.91; N, 5.05. Found: C, 65.51; H, 7.20; N, 5.07.

Acknowledgment.—Spectral data were determined by Mr. W. Fulmor and staff, and microanalyses were furnished by Mr. L. Brancone and associates. Partition chromatography was performed by Mr. C. Pidacks and staff. We are indebted to Mr. A. C. Dornbush and associates for *in vitro* antibacterial assays.

(8) For a complete description of this technique as developed by C. Pidacks see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

A Polymeric Nitrofuran Derivative with Prolonged Antibacterial Action[1a]

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Recently some attempts have been reported to obtain polymers possessing pharmacological activity. Besides studies involving the preparation of polymeric models of natural macromolecules (with more or less known pharmacological activity), polymers have been sought, whose monomeric units were endowed *per se* with some pharmacological activity, because of the groupings present in them. The general aim was to obtain macromolecules which would, at least partially, retain the activity of the monomer. A slow liberation of monomeric units *in vivo* might lead to a prolongation of action, and thereby attain drug latentiation.[2]

Such macromolecular drugs may, of course, show inherent new physiological activities and a characteristic toxicity of their own. This has been noticed for some specific polymers which induce renal lesions.[3] A

(1) (a) Research supported by funds of Consiglio Nazionale della Ricerche, Rome, Italy. (b) To whom inquiries should be addressed.

(2) N. J. Harper, *Progr. Drug Res.*, **4**, 221 (1962).

(3) C. Vaille, C. Debray, E. Martin, M. Souchard, and C. Roze, *Ann. Pharm. Franc.*, **20**, 409 (1962); *Chem. Abstr.*, **57**, 14381 (1962).