Studies on the Synthesis of Heterocyclic Compounds containing Benzopyrone. Part 4.[1] Synthesis of 4,10-Dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one, the Basic Skeleton in Fulvic Acid

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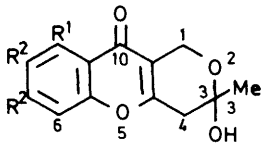
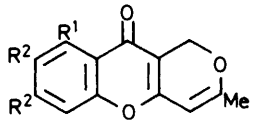
The synthesis of 4,5-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**1b**), the basic skeleton in fulvic acid, is described. The acetal (**4**), chosen as a common intermediate for syntheses of the basic skeletons in fungal metabolites such as fulvic acid and citromycetin, was cyclized into the dihydropyrone (**7**) with 5% HCl–tetrahydrofuran (1 : 2) regioselectively. Debenzylation followed by cyclization of the boron complex of (**7**) gave the tricyclic pyrone [**2b**], which was converted into the benzopyranone (**1b**) with 5% HCl–acetone (1 : 1).

During the course of our studies on the syntheses of heterocyclic compounds containing benzopyrone[1,2] we initiated a program centred on the total synthesis of fungal metabolites such as fulvic acid (**1a**)[3] and citromycetin (**3a**).[4] In our preliminary



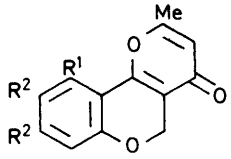
(**1**)

a; $R^1 = CO_2H$, $R^2 = OH$
b; $R^1 = R^2 = H$
c; $R^1 = CO_2Me$, $R^2 = OMe$



(**2**)

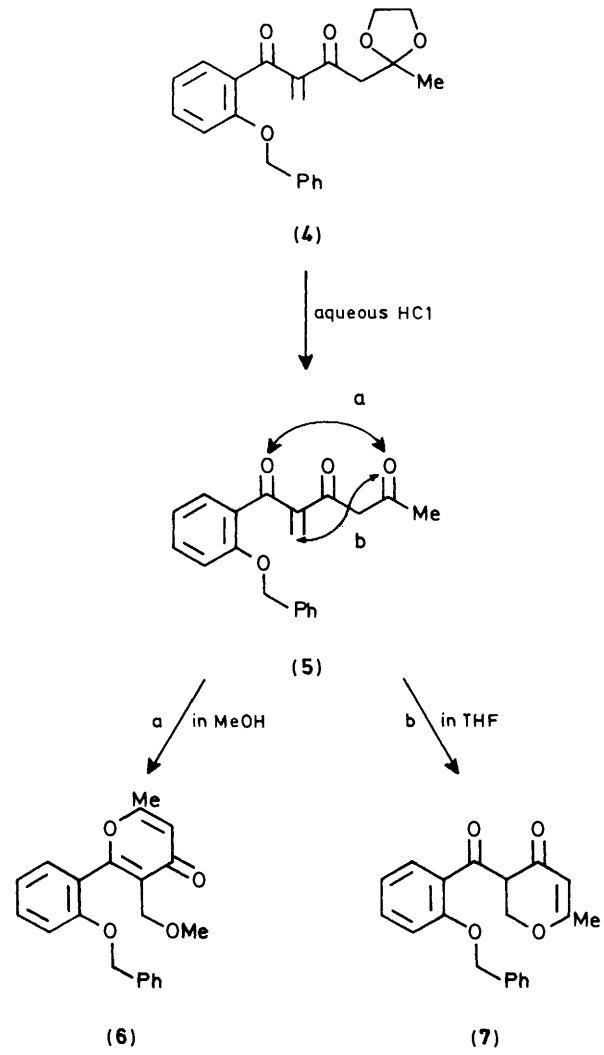
a; $R^1 = CO_2H$, $R^2 = OH$
b; $R^1 = R^2 = H$



(**3**)

a; $R^1 = CO_2H$, $R^2 = OH$
b; $R^1 = R^2 = H$

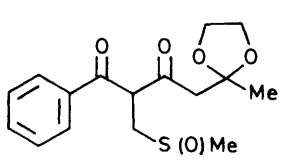
studies we have investigated the syntheses of the basic skeletons in these metabolites. In a previous paper[1] we described the synthesis of 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**3b**), the basic skeleton in citromycetin (**3a**), *via* biogenetic type condensation of the acetal (**4**) to give the pyrone (**6**). It was thought that the cyclization was initiated by the Michael-type addition of methanol to the α,β-unsaturated ketone followed by condensation between the benzoyl group and the acetyl group to give (**6**) (path a). In a relatively weak nucleophilic solvent cyclization of the acetal (**4**) may be expected to proceed *via* the alternative path to yield the pyrone (**7**). In fact, the condensation between the ene moiety and the acetyl ketone in



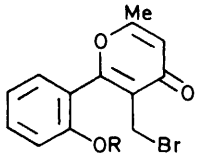
Scheme 1.

the acetal (**4**) was realized in hydrochloric acid–tetrahydrofuran. In this paper we report the synthesis of 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**1b**),[5] the basic skeleton in fulvic acid (**1a**).

The acetal (**4**),[1] obtained by pyrolysis of the sulphinyl compound (**8**),[1] was treated with 5% HCl–tetrahydrofuran



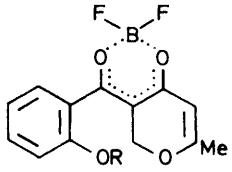
(8)



(9)

a ; R = CH_2Ph

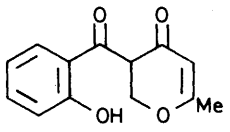
b ; R = H



(10)

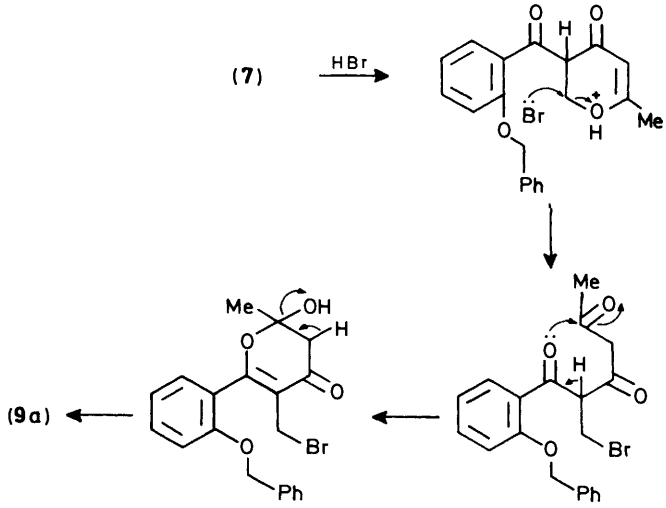
a ; R = CH_2Ph

b ; R = H



(11)

(1:2) at ambient temperature for 24 h to give the pyrone (**7**) as a single cyclization product in 97% yield. More conveniently, the pyrone (**7**) was obtained by treating (**8**) with 5% H_2SO_4–AcOH–THF (1:1:4) under reflux for 1 h in 97% yield. Structure (**7**) was confirmed by (i) a positive $FeCl_3$ test, (ii) presence of the ion *m/z* 322 (M^+), and (iii) characteristic ^1H n.m.r. signals for 2,3-dihydro-4*H*-pyran-4-one [δ 4.63 (2-H) and 5.32 (5-H)].[6] With the pyrone (**7**) in hand we examined the hydrogenolysis of the benzyl group. Initial hydrogenolysis of (**7**) with palladium–carbon gave complex and unidentified products, probably as a result not only of cleavage of the benzyl group but also the pyrone ring. With dry hydrogen bromide in acetic acid the pyrone (**7**) gave the bromide (**9a**), the structural assignment of which was made on the basis of a characteristic dienone olefinic proton signal (δ 6.20)[7] and the presence of the ions *m/z* 386 ($M^+ + 2$) and 384 (M^+). Further evidence was obtained from the fact that debenzylation of (**9a**) gave the phenol (**9b**), the synthesis of which has been reported previously.[1] The rearrangement of the pyrone (**7**) into the bromide (**9a**) can be explained by the reaction mechanism shown in Scheme 2: (i) Protonation of the oxygen atom in the dihydropyran ring and spontaneous ring opening followed by nucleophilic bromide attack on the α-carbon; (ii) recyclization between the benzoyl carbonyl group and acetyl carbonyl group; and (iii) dehydration. Since (**9b**) was converted quantitatively into 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**3b**),[1] the basic skeleton in citromycetin, this route [*via* (9a)] is an alternative preparation of (**3b**). Last, treatment of (**7**) with BF_3·OEt_2–Me_2S–CH_2Cl_2 (Fujita's method)[8] gave the debenzylated boron complex (**10b**) in *ca.* 15% yield instead of the phenol (**11**). These facts suggest that prior formation of the boron complex (**10a**) would improve the yield of the debenzylation product (**10b**). In fact, the pyrone (**7**) afforded the boron complex (**10a**) in 70% yield on treatment with boron trifluoride–diethyl ether in dichloromethane. Although catalytic hydrogenation of (**10a**) with palladium–carbon gave an unidentified complex product, application of Fujita's method[8] to (**10a**) afforded (**10b**) in 88% yield.



Scheme 2.

Treatment of (**10b**) with concentrated HCl–acetic acid (1:10) resulted in the cleavage of the boron–oxygen ring and cyclization between the pyrone carbonyl group and phenol to give the pyranobenzopyran (**2b**) in 79% yield. The ^1H and ^{13}C n.m.r. spectra [δ 2.02 (Me), 5.32 (CH_2), and 5.45 (=CH); δ_C 20.3 (Me), 64.9 (1-C), 94.7 (4-C), 102.7 (10a-C), 159.9 (4a-C), 167.8 (3-C), and 173.5 (10-C)] had similarities to those* of dehydrofulvic acid (**2a**). Although the conversion of dehydrofulvic acid (**2a**) into fulvic acid (**1a**) has been achieved by treating with 1M-H_2SO_4,[3c] this method might not be applied to the pyranobenzopyran (**2b**) owing to its insolubility in water. Somewhat modified treatment of (**2b**) with 5% HCl–acetone (1:1) at ambient temperature[9] for 4 days afforded 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**1b**), the basic skeleton in fulvic acid (**1a**), in 78% yield. The spectral data for (**1b**) [$\nu_{max.}$ 3 300, 1 645, and 1 595 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 226 (4.44), 265 (3.89), and 297 nm (3.93); δ_H 1.57 (Me), 2.79 (2H,ABq, *J* 17.6 Hz, 4-H), 4.65 (2H, s, 1-H), 7.32–7.81 (3H, m, 6-, 7-, 8-H), and 8.11 (1H, dd, *J* 8.3 1.5 Hz, 9-H); δ_C 28.6 (Me), 38.0 (4-C), 56.9 (1-C), 115.8 (10a-C), 160.3 (4a-C), and 175.6 (10-C)] closely resembled those reported† for fulvic acid (**1a**) and methyl *O*,*O*-dimethylfulvate (**1c**). The pyranobenzopyran (**1b**) was also obtained by treating (**2b**) with (i) $Hg(OAc)_2$, (ii) $NaBH_4$, and (iii) KI[10] but in low yield. Recently Dean *et al*[11] have succeeded in the synthesis of this ring system from chromones *via* three routes. Application of our method to suitably substituted acetophenone would lead to the total synthesis of fulvic acid (**1a**).

Experimental

M.p.s and b.p.s are uncorrected and extracts were dried over $MgSO_4$. I.r. spectra were recorded on a Hitachi Model 215 spectrophotometer. U.v. spectra were recorded with a Hitachi Model 200—10 spectrophotometer. Mass spectra were taken on a Shimazu LKB-9000 mass spectrometer and high-resolution mass spectra with a JEOL JMS-OlSG instrument. ^1H N.m.r.

* (*a*) For the ^1H n.m.r. spectrum of (**2a**) see F. M. Dean and D. R. Randell, *J. Chem. Soc.*, 1961, 798; (*b*) for ^{13}C n.m.r. spectrum see I. Kurobane, C. R. Hutchinson, and L. C. Vining, *Tetrahedron Lett.*, 1981, **22**, 493.

† For the i.r. and u.v. spectra of (**1a**) see ref. 3*c*; for the ^{13}C n.m.r. spectrum of (**1a**) see footnote *(*b*); for the ^1H n.m.r. spectrum of (**1a**) see T. Sakai, A. Ichihara, and S. Sakamura, *Agric. Biol. Chem.*, 1981, **45**, 1275.

spectra were obtained with a JEOL 100 spectrometer and ^{13}C n.m.r. spectra with a JEOL JMN-GX 270 spectrometer (tetramethylsilane as internal reference).

3-(2-*Benzyloxybenzoyl*)-6-*methyl*-2,3-*dihydro*-4H-*pyran*-4-*one* (**7**).—*Method A*. A solution of the enedione (**4**) (829 mg) in 5% HCl–tetrahydrofuran (1:2) (90 ml) was stirred at ambient temperature for 48 h. The reaction mixture was poured into ice–water (30 ml), and extracted with benzene (3 × 30 ml), dried, and evaporated to yield 3-(2-benzyloxybenzoyl)-6-methyl-2,3-dihydro-4*H*-pyran-4-one (**7**) (707 mg, 97%). This pyrone was too unstable to be purified by column chromatography or distillation; *m/z* 322 (M^+); $\nu_{max.}$ (neat) 1605 cm^{-1}; δ($CDCl_3$) 1.92 (3 H, s, Me), 4.63 (2 H, s, 2-H), 5.05 (2 H, s, OCH_2Ph), 5.32 (1 H, s, =CH), and 6.80—7.63 (9 H, m, ArH).

Method B. A mixture of the 1,3-dione (**8**) (1.28 g), 5% H_2SO_4 (12.5 ml), AcOH (12.5 ml), and tetrahydrofuran (50 ml) was refluxed for 1 h under an argon atmosphere. After being cooled the reaction mixture was poured into ice–water (100 ml) and extracted with ether (2 × 50 ml). The organic layer was washed with water (5 × 30 ml), dried, and evaporated to afford the pyrone (**7**) (0.93 g, 97%).

2-(2-*Benzyloxyphenyl*)-3-*bromomethyl*-6-*methyl*-4H-*pyran*-4-*one* (**9a**).—To a solution of the pyrone (**7**) (540 mg) in AcOH (5 ml) was added 4% (w/w) HBr in AcOH at 0 °C. The reaction mixture was stirred at ambient temperature for 24 h, then poured into ice–water (10 ml) and extracted with CH_2Cl_2–Et_2O (1:4) (3 × 25 ml). The organic layer was washed with water (3 × 10 ml), dried, and evaporated. The resulting residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck, 5% AcOEt in benzene as eluant) to give 2-(2-benzyloxyphenyl)-3-bromomethyl-6-methyl-4*H*-pyran-4-one (**9a**) (231 mg, 36%); *m/z* 386 ($M^+ + 2$) and 384 (M^+); $\nu_{max.}$ ($CHCl_3$) 1 660, 1 612, and 1 602 cm^{-1}; δ($CDCl_3$) 2.23 (3 H, s, Me), 4.14 (2 H, s, CH_2Br), 5.12 (2 H, s OCH_2Ph), 6.20 (1 H, s, =CH), and 6.92—7.63 (9 H, m, ArH).

3-*Bromomethyl*-2-(2-*hydroxyphenyl*)-6-*methyl*-4H-*pyran*-4-*one* (**9b**).—A solution of the pyranone (**9a**) (26 mg, 0.07 mmol) in 35% (w/w) HBr–AcOH (3 ml) was stirred for 24 h at ambient temperature. The reaction mixture was poured into ice–water (5 ml) and extracted with a mixture of CH_2Cl_2– Et_2O (2:5) (3 × 20 ml). The organic layer was washed with water (5 × 10 ml), dried, and evaporated. Recrystallization of the residue from benzene gave 3-bromomethyl-2-(2-hydroxyphenyl)-6-methyl-4*H*-pyran-4-one (**9b**), which was identical with the sample[1] reported previously.

BF_2 *Complex of* 3-(2-*Benzyloxybenzoyl*)-2,3-*dihydro*-6-*methyl*-4H-*pyran*-4-*one* (**10a**).—A solution of the pyranone (**7**) (999 mg) in anhydrous CH_2Cl_2 (10 ml) was added to a solution of BF_3·OEt_2 (1 ml) in CH_2Cl_2 (33 ml) at 0 °C under an argon atmosphere. The stirring was continued at ambient temperature for 4.5 h after which the reaction mixture was poured into ice–water (100 ml) and extracted with Et_2O–AcOEt (5:1) (3 × 40 ml). The organic layer was washed with water (3 × 100 ml), dried, and evaporated. The resulting residue was subjected to column chromatography (Florisil, Wako, benzene as eluant) to give the BF_2 complex of the pyrone (**10a**) (615 mg, 70%); m.p. 114—115 °C (from benzene) (Found C, 65.1; H, 4.6. $C_{20}H_{17}BF_2O_4$ requires C, 64.89; H, 4.64%); $\nu_{max.}$ (KBr) 1 597sh, and 1 593 cm^{-1}; $\lambda_{max.}$ (EtOH) 263 (log ε 4.00) and 369 nm (4.03); δ ($CDCl_3$) 2.04 (3 H, s, Me), 4.87 (2 H, s, OCH_2, 5.09 (2 H, s, OCH_2Ph), 5.62 (1 H, s, =CH), and 7.01—7.60 (9 H, m, ArH); δ_C [$(CD_3)_2SO$] 21.5, 67.9, 70.1, 99.1, 99.8, 113.7, 121.4, 121.7, 127.8, 128.7, 130.0, 133.8, 136.6, 155.8, 171.7, 178.7, and 184.8 p.p.m.

BF_2 *Complex of* 3-(2-*hydroxybenzoyl*)-2,3-*dihydro*-6-*methyl*-4H-*pyran*-4-*one* (**10b**).—A solution of the benzyloxy compound (**10a**) (160 mg, 0.43 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of Me_2S (1.5 ml), BF_3·OEt_2 (0.5 ml) in CH_2Cl_2 (10 ml) at −20 °C under an argon atmosphere. The reaction mixture was stirred for 24 h at ambient temperature and then poured into cooled aqueous NaCl (20 ml) and extracted with Et_2O (3 × 20 ml). The ether layer was washed with aqueous NaCl solution (5 × 5 ml), dried, and evaporated to afford the BF_2 complex of 3-(2-hydroxybenzoyl)-6-methyl-2,3-dihydro-4*H*-pyran-4-one (**10b**) (106 mg, 88%), m.p. 137—139.5 °C (from benzene–ethanol) (Found: C, 55.6; H, 3.8. $C_{13}H_{11}BF_2O_4$ requires C, 55.75; H, 3.97% $\nu_{max.}$ (KBr) 3 500, 1 610, 1 600, and 1 560 cm^{-1}; $\lambda_{max.}$ (EtOH) 262 (log ε 3.66) and 378 nm (4.07); δ($CDCl_3$) 2.20 (3 H, s, Me), 5.20 (2 H, s, CH_2), 5.74 (1 H, s, =CH), and 6.90—7.53 (4 H, m, ArH); δ_C [$(CD_3)_2SO$] 21.6, 68.1, 99.8, 99.9, 116.8, 120.0, 129.9, 133.8, 155.8, 172.3, 178.5, and 184.4 p.p.m.

3-*Methyl*-1H,10H-*pyrano*[4,3-b][1]*benzopyran*-10-*one* (**2b**).—A mixture of the BF_2 complex (**10b**) (106 mg, 0.38 mmol), AcOH (3 ml), and concentrated HCl (0.3 ml) was stirred for 3 h at ambient temperature. The reaction mixture was poured into ice–water (30 ml), and extracted with benzene (3 × 10 ml). The benzene layer was washed with water (5 × 5 ml), dried, and evaporated. The resulting residue was subjected to preparative centrifugal t.l.c. (Kieselgel 60 PF_{254}, Merck, CH_2Cl_2 as eluant) to give 3-methyl-1*H*,10*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**2b**) (64 mg, 79%), m.p. 59.5—61.5 °C (from n-hexane–benzene) (Found: C, 72.8; H, 4.8. $C_{13}H_{10}O_3$ requires C, 72.88; H, 4.71%); *m/z* 214 M^+; $\nu_{max.}$ (KBr) 1 656, 1 594, and 1 554 cm^{-1}; $\lambda_{max.}$ (EtOH) 250 (log ε 4.22), 302 (4.03), and 346 nm (4.13); δ ($CDCl_3$) 2.02 (3 H, s, Me), 5.32 (2 H, s, CH_2), 5.45 (1 H, s, =CH), and 7.27—7.67 (3 H, m, ArH); δ_C ($CDCl_3$) 20.3, 64.9, 94.7, 102.7, 117.7, 124.7, 125.5, 132.7, 155.4, 159.9, 167.8, and 173.5 p.p.m.

4,10-*Dihydro*-3-*hydroxy*-3-*methyl*-1H,3H-*pyrano*[4,3-b][1]-*benzopyran*-10-*one* (**1b**).—*Method A*. A mixture of the benzopyranone (**2b**) (76 mg, 0.35 mmol) and 5% aqueous HCl (5 ml) in acetone was stirred for 4 days at ambient temperature. The reaction mixture was poured into ice–water (10 ml) and extracted with AcOEt (3 × 10 ml). The ethyl acetate layer was washed with water (3 × 5 ml), dried, and evaporated. The resulting residue was subjected to preparative centrifugal t.l.c. (Kieselgel 60 PF_{254}, Merck, CH_2Cl_2–AcOEt (7:3) as eluant) to give unchanged (**2b**) (11 mg). Further elution gave 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**1b**) [55 mg, 69%; 78% from reacted (**2b**)], m.p. 182—183.5 °C (from dioxane) (Found: C, 66.5; H, 5.0. $C_{13}H_{12}O_4$ requires C, 67.22; H, 5.22%); *m/z* 232.0726 (M^+) ($C_{13}H_{12}O_4$ requires M^+, 232.0735); $\nu_{max.}$ (KBr) 3 300, 1 645, and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 265 log ε (3.82), 296 (3.86), and 302 nm (3.86); δ [$CDCl_3$–$(CD_3)_2SO$, 3:1] 1.57 (3 H, s, Me), 2.79 (2 H, ABq, *J* 17.6 Hz, CH_2), 4.65 (2 H, s, OCH_2), 7.32—7.81 (3 H, m, ArH), and 8.11 (1 H, dd, *J* 8.3, 1.5 Hz, 9-H); δ_C [$CDCl_3$–$(CD_3)_2SO$, 3:1) 28.6, 38.0, 56.9, 94.7, 115.8, 118.1, 125.0, 125.5, 133.6, 156.5, 160.3, and 175.6 p.p.m.

Method B. A mixture of the benzopyranone (**2b**) (35 mg, 0.16 mmol), $Hg(OAc)_2$ (58 mg, 0.18 mmol), water (2 ml), and tetrahydrofuran (8 ml) was stirred at 0 °C for 30 min. A solution of $NaBH_4$ (9 mg) in water (1 ml) and a solution of KI (150 mg) in water (1 ml) at −10 °C were then added to the reaction mixture which was then poured into saturated aqueous NaCl (5 ml) and extracted with benzene. The benzene layer was washed with aqueous NaCl (3 × 5 ml), dried, and evaporated. The residue was subjected to preparative centrifugal t.l.c. (Kieselgel 60 PF_{254}, Merck, CH_2Cl_2–AcOEt 7:3 as eluant) to give 4,10-

dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]-benzopyran-10-one (**1b**) (14 mg, 37%).

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