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REARRANGEMENT OF SPIROBENZYLISOQUINOLINE TO PROTOBERBERINE SYSTEMS

A COMPARISON OF BASE INDUCED AND PHOTOCHEMICAL PROCESSES

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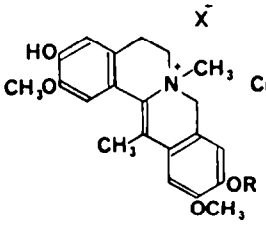
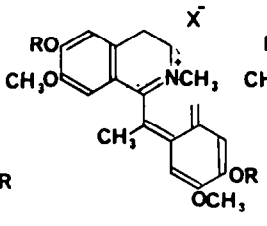
Abstract—It has been found that the spirobenzylisoquinoline ketones (**14** and **17**) rearrange to the corresponding dihydroprotoberberin-8-ones (**21** and **22**) on treatment with strong base. A mechanism is proposed for the process which involves an aziridinol intermediate. The complementary photochemical rearrangement of **17** has been studied under neutral and acid conditions which produce **24** and **25** respectively.

In recent years there has been much interest in the rearrangement of 13-methyl and 13-oxoprotoberberinium metho salts to spirobenzylisoquinolines which may be exemplified by the processes (**1–2–3**)[1] and (**4–5–6**).[2] The likely intermediate **5** in the second example has the requisite enolate and imonium systems for such a cyclisation incorporated into an azatriene which, at the same time, has the potential for cyclisation to the enolate of **4**. The elegant studies by Kametani[3] utilising 1-benzocyclobutenylisoquinolinium salts (**7**) as a source of the azatriene system,[8] analogous to **2**, show the delicate balance between concerted cyclisation to the protoberberine system (**9**) or a spirobenzylisoquinoline (**10**). Photocyclisation of enamides, e.g. **11** has been employed to synthesise 8-oxopalmatine (**13**) via cyclisation of the azatriene system (**12**) implicit in the enamide structure.[4]

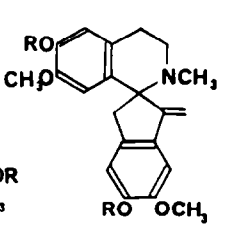
Due to the facile synthesis[5] of spirobenzylisoquinolines of the type **14** from the corresponding phenethylamine



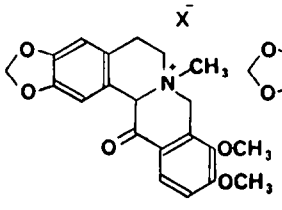
1, R = H
26, R = CH_3



2, R = H
8, R = CH_3



3, R = H
10, R = CH_3



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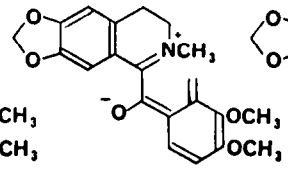

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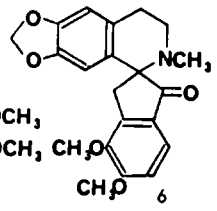

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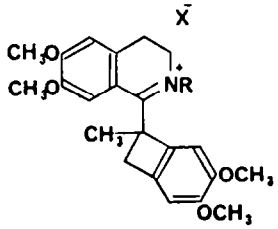

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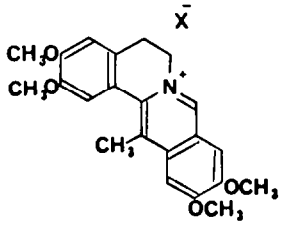

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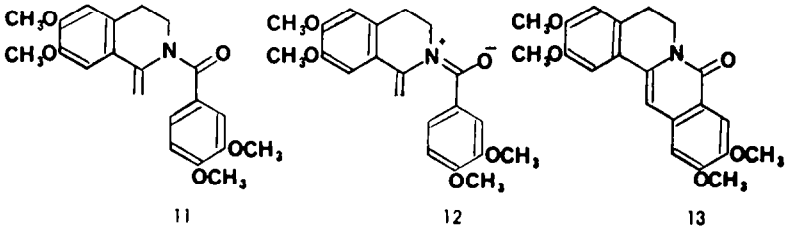
and indan-1,2-dione it was decided to investigate the use of spirobenzylisoquinoline ketones as precursors of protoberberine systems. The substrate chosen for rearrangement studies was **17** which was synthesised from the readily accessible **14**[5] by the sequence **14–15–16–17**. This procedure proved to be very efficient and avoided the more direct route from **14** to **17** by CH_2N_2 treatment which is accompanied by N-methylation leading to **18**.[6]

This unusual N-methylation of **17** by CH_2N_2 is probably due to stereoelectronic factors resulting from the proximity of the NH to the CO group in the rigid structure. It was considered that this would favour the formation of aziridinol intermediates **19** and **20** from **14** and **17** respectively. These aziridinols, or more accurately the anions derived therefrom, could reasonably be expected to fragment under strongly basic conditions to the dihydroprotoberberin - 8 - ones (**21** and **22**) since this process would involve the generation of an intermediate having a lactam function and a stabilised carbanion which would subsequently be protonated.[7] In the case of simple analogues, in which the carbanion is not stabilised, cleavage of lithio derivatives of aziridinols derived from aziridinones and RLi affords the alternative mode of fission leading to amino ketonic products.[8] Shamma and Nugent[9] have proposed the intermediacy of **27** in the rearrangement of the dihydroprotoberberine salt (**26**) to the dibenzocyclopent[b]azepine (**28**). In this case the aziridinium bond cleavage is dictated by the relationship of the charged centres of **27** in the drive towards neutrality in the next intermediate along the reaction path.

Treatment of **17** with strong base (KOBu^t–DMSO) afforded the lactam **22** both under anhydrous conditions and in the presence of H_2O as recommended by Gassman[10] for the cleavage of non-enolisable ketones. The ketones **14** and **17** used in this study are, of course, capable of enolisation, although this would occur at the expense of aromatic stabilisation. A small amount of the dehydro compound (**24**) was observed from UV and NMR spectroscopic examination during isolation of **22**, which may be due to aerial oxidation of **22** or the intermediate carbanion. This occurence was more serious with the phenolic analogue (**14**) which gave the desired lactam (**21**) in lower yield. TLC and NMR examination of the crude material from this reaction indicated a mixture of **21** and **23**. It could easily be shown that **21** was susceptible to facile out oxidation in solution. The analogue **18** gave no discernible products on treatment with KOBu^t–DMSO which may be explained by N-substitution which would preclude formation of an aziridinol intermediate.

Irie *et al.*[6] have shown that irradiation of **17** (high pressure Hg lamp–THF) yields a mixture of **24** (minor component) and the protoberberine (**25**) which was characterised as the $NaBH_4$ reduction product. Thus it would appear that basic and photochemical methods of rearrangement of spirobenzylisoquinoline ketones, such as **17**, could be complementary and lead specifically to systems like **22**, **24** and **25**. It was therefore decided to investigate the photolysis conditions necessary for



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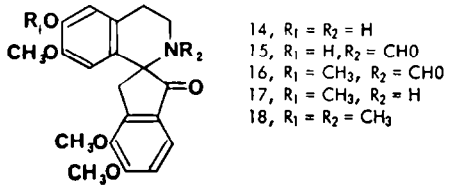
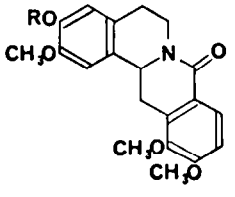
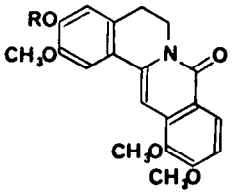


14, $R_1 = R_2 = H$
15, $R_1 = H, R_2 = CHO$
16, $R_1 = CH_3, R_2 = CHO$
17, $R_1 = CH_3, R_2 = H$
18, $R_1 = R_2 = CH_3$

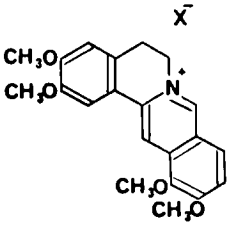
19, R = H
20, R = CH_3



21, R = H
22, R = CH_3



23, R = H
24, R = CH_3



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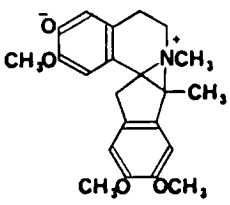

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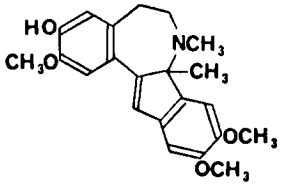

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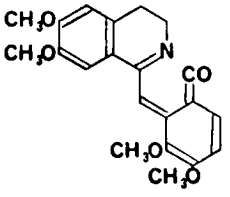

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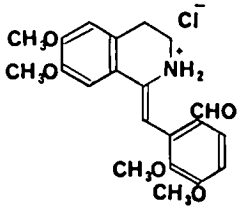

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controlled production of **24** and **25**. Irradiation of **17** under a N_2 atmosphere in Et_2O using a medium pressure Hg vapour lamp and a quartz apparatus afforded the unsaturated lactam **24** in 30% overall yield. Comparison of the spectral data of **22** and **24** clearly showed the effects due to the **13**, **14** double bond in the latter. Then the irradiation was performed on **17** in Et_2O–MeOH (5:1) in the presence of excess HCl the major product (28%) was assigned the protoberberine hydroxide structure (**29**; X = OH) which was strongly supported by the UV spectra in neutral and basic solution.[11,12] On treatment with conc KOH **25** disproportionated into the dihydroberberine and **24** which could be identified by its characteristic UV spectrum. Thus the generation of the photolysis products of Irie *et al.*[6] may be greatly influenced by pH. It would seem reasonable that the photochemical reaction of **17** in neutral solution proceeds via a Norrish type I process leading to the azatriene system (**29**) which would cyclise spontaneously to **24** by analogy with the researches discussed earlier. On the other hand the photochemical process which occurs in acid solution requires the intermediate (**30**) resulting from Norrish-type I cleavage followed by a 1,5 hydrogen transfer.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined using a Unicam SP200 and UV spectra determined using a Unicam SP800 spectrometer. Mass spectra were obtained from A.E.I. MS12 and MS902 instruments (the latter with on-line computer). NMR spectra were obtained using Varian A-60 or HA 100 spectrometers.

6 - *Hydroxy* - 7 - *methoxy* - N - *formyl* - 1,2,3,4 - *tetrahydroisoquinoline* - 1 - *spiro* - 2' - (4',5' - *dimethoxy* - 1' - *indanone*), **15**. Ac_2O (5.4 ml, 48 mmole) was added dropwise to a soln of **14**[5] (3 g, 9 mmole) in 98% HCOOH (16.8 ml, 0.42 mole) kept at <50°. The soln was heated at 50° for 15 min, then stirred at room temp. for 4 hr whereupon the mixture was poured into ice-water. The ppt was filtered off and washed (H_2O) to give the crude product which was crystallised from Et_2O–EtOAc–$CHCl_3$ to give **15** (2.7 g, 85%) m.p. 215°, ν_{max} ($CHCl_3$) 3520, 1710, 1662 cm^{-1}; λ_{max} (EtOH) 286 (13,740), 232 nm (ϵ 18,340); NMR ($CDCl_3$) δ 3.0–3.9 (m, 4H), 3.48 (s, 3H), 3.62 (s, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 5.02 (brs, H), 6.15 (s, H), 6.66 (s, H), 7.02 (d, H, J = 8 Hz), 7.60 (d, H, J = 8 Hz), 8.20 (s, H); *m/e* 383,355 (P–CO). (Found: C, 65.60; H, 5.36; N, 3.74. $C_{21}H_{21}NO_6$ requires: C, 65.80; H, 5.48; N, 3.65%).

6,7 - *Dimethoxy* - N - *formyl* - 1,2,3,4 - *tetrahydroisoquinoline* - 1 - *spiro* - 2' - (4',5' - *dimethoxy* - 1' - *indanone*), **16**. A soln of **15** (2.7 g, 7 mmole), and Me_2SO_4 (4.7 g, 37 mmole) in dry acetone (200 ml) together with K_2CO_3 (5 g, 36 mmole) was stirred under reflux for 5 hr. The mixture was filtered and the filtrate concentrated *in vacuo* to give a residue which was dissolved in $CHCl_3$, washed with $NaHCO_3$ aq, H_2O then dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a crude product which was crystallised from EtOAc–Et_2O to give **16** (2.1 g, 80%) m.p. 178°, ν_{max} ($CHCl_3$) 1720, 1660 cm^{-1}; λ_{max} (EtOH) 287 (12, 140), 228 nm (ϵ 14,700); NMR ($CDCl_3$) δ 3.8–4.0 (m, 4H), 3.49 (s, 3H), 3.66 (s, 2H), 3.82 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 6.20 (s, H), 6.68 (s, H), 7.05 (d, H, J = 8 Hz), 7.60 (d, H, J = 8 Hz), 8.22 (s, H); *m/e* 397, 369 (P–CO). (Found: C, 66.56; H, 5.78; N, 3.74. $C_{22}H_{23}NO_6$ requires: C, 66.49; H, 5.79; N, 3.53%).

6,7 - *Dimethoxy* - 1,2,3,4 - *tetrahydroisoquinoline* - 1 - *spiro* - 2' - (4',5' - *dimethoxy* - 1' - *indanone*), **17**. The N-formyl derivative **16** (1.8 g, 4.5 mmole) in H_2O–MeOH–conc HCl (2:2:1) was heated under reflux for 5 hr. After cooling, the soln was neutralised with sat $NaHCO_3$ aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed (H_2O), dried (Na_2SO_4) then concentrated *in vacuo* to give a gum (1.62 g) which was chromatographed on grade III alumina (45 g). Elution with benzene–EtOAc (3:1) afforded **17** as a very viscous oil (1.52 g, 90%), ν_{max} ($CHCl_3$) 1690, 1590 cm^{-1}; λ_{max} (EtOH) 288 (15,680), 226 nm (ϵ 17,140); NMR($CDCl_3$) δ 2.60–3.35 (m, 5H), 3.48 (s, 2H), 3.59 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 3.99 (s, 3H), 6.14 (s, H), 6.63 (s, H), 7.07 (d, H, J = 8 Hz), 7.67 (d, H, J = 8 Hz); *m/e* 369.1573 ($C_{21}H_{23}NO_5$ requires: 369.1576), 354.1335 ($C_{20}H_{20}NO_5$ requires: 354.1341), 341.1608 ($C_{20}H_{23}NO_4$ requires: 341.1626), 340.1208 ($C_{19}H_{18}NO_5$ requires: 340.1184), 310.1461 ($C_{19}H_{20}NO_3$ requires: 310.1443); HCl salt m.p. 151–2°; picrate m.p. 125–6° (lit.[6] m.p. 123–4°).

6,7 - *Dimethoxy* - N - *methyl* - 1,2,3,4 - *tetrahydroisoquinoline* - 1 - *spiro* - 2' - (4',5' - *dimethoxy* - 1' - *indanone*), **18**. A soln of **17** (2.19 g, 5.3 mmole) in 98% HCOOH (10.56 ml, 0.28 mole) and 37% HCHO (10.56 ml, 0.17 mole) was stirred at 95° for 4 hr. After cooling, H_2O (50 ml) was added and the soln neutralised with 0.88 NH_3 followed by extraction with $CHCl_3$. The $CHCl_3$ soln was worked up as described in the previous experiment to give a gum which was chromatographed over grade III alumina (60 g). Elution with benzene–EtOAc (3:1) afforded **18** as a viscous oil (1.95 g, 86%); ν_{max} ($CHCl_3$) 1695, 1595 cm^{-1}; λ_{max} (EtOH) 282 (17,000), 221 nm (ϵ 15,000); NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.7–3.2 (m, 3H), 3.40–3.60 (s + m, 6H), 3.88 (s, 3H), 4.00 (s, 3H), 4.05 (s, 3H), 6.20 (s, H), 6.70 (s, H), 7.12 (d, H, J = 8 Hz), 7.70 (d, H, J = 8 Hz); *m/e* 383.1726 ($C_{22}H_{25}NO_5$ requires: 383.1732), 368.1489 ($C_{21}H_{22}NO_5$ requires: 368.1497), 354.1725 ($C_{21}H_{24}NO_4$ requires: 354.1705), 340.1543 ($C_{20}H_{22}NO_4$ requires: 340.1548); picrate m.p. 137–8°.

2,3,11,12 - *Tetramethoxy* - 13,14 - *dihydroprotoberberin* - 8 - *one*, **22**. To a soln of **17** (478 mg, 1.3 mmole) in dry DMSO (10 ml) under a N_2 atmosphere was added H_2O (50 μl) followed by careful addition of freshly sublimed $KOBu^t$ (1.13 g, 10 mmole). The mixture was stirred for 1 hr under a N_2 atmosphere then diluted with H_2O (20 ml). A white solid was filtered and crystallised from EtOAc to give **22** (115 mg). Evaporation of the mother liquors *in vacuo* gave a pale yellow gum (155 mg).

The aqueous filtrate of the mixture was extracted with Et_2O then EtOAc and the combined extracts washed with H_2O then dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a gum which was combined with the above 155 mg and chromatographed over grade III alumina (12 g). Elution with benzene–$CHCl_3$ (5:2) yielded a viscous oil (112 mg) which was crystallised from EtOAc to give **22** (80 mg; total yield 195 mg, 41%), m.p. 179–180°; ν_{max}

($CHCl_3$) 1620, 1580 cm^{-1}; λ_{max} (EtOH) 359 (3,000), 350 (4,300), 330 (4,000), 264 (18,600), 220 nm (ϵ 20,600); NMR ($CDCl_3$) δ 2.5–3.0 (m, 4H), 3.56 (q, H, J = 4 Hz), 3.80 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 4.71 (q, H, J = 4 Hz), 4.94 (q, H, J = 4 Hz), 6.67 (s, H), 6.74 (s, H), 6.91 (d, H, J = 8 Hz), 7.91 (d, H, J = 8 Hz). (Found: C, 68.50; H, 5.99; N, 3.90. $C_{21}H_{23}NO_5$ requires: C, 68.29; H, 6.23; N, 3.79%).

Repeat of the above experiment without the addition of H_2O gave identical results. When **18** was used in this reaction only starting material was recovered.

3 - *Hydroxy* - 2,11,12 - *trimethoxy* - 13,14 - *dihydroprotoberberin* - 8 - *one*, **21**. The above reaction was repeated using **14** (1.2 g, 34 mmole), H_2O (140 μl), KOBu^t (3.24 g, 46.1 mmole) in DMSO (31 ml). After 1.5 hr at room temp. under a N_2 atmosphere, H_2O (40 ml) was added and the pH adjusted to 7. The mixture was worked up as above to give a crude product (941 mg) which was chromatographed over grade III alumina (75 g). Elution with benzene–EtOAc (3:2) yielded a pale yellow oil (540 mg). The NMR spectrum indicated a mixture of **21** and **23** which was again subjected to chromatography (grade III alumina, 25 g) to afford a viscous oil (311 mg) on elution with benzene–EtOAc (2:1). Crystallisation from EtOAc–Et_2O gave **21** (242 mg, 20%) m.p. 169°; ν_{max} ($CHCl_3$) 3500, 1635, 1600 cm^{-1}; λ_{max} (EtOH) 360 (3,300), 352 (6,250), 340 (5,675), 264 (15,630), 224 nm (ϵ 18,320); NMR ($CDCl_3$) δ 2.82 (m, 4H), 3.78 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H) 4.75 (m, 2H), 6.78 (s, 2H), 6.94 (d, H, J = 8 Hz), 7.95 (d, H, J = 8 Hz). (Found: C, 67.66; H, 6.25; N, 3.85. $C_{20}H_{21}NO_5$ requires: C, 67.59; H, 5.96; N, 3.94%).

Solns of **21** in organic solvents were found to be readily susceptible to aerial oxidation to mixtures of **21** and **23**.

2,3,11,12-*Tetramethoxyprotoberberin*-8-*one*, **24**. Et_2O (300 ml) was added to a soln of **17** (350 mg, 0.95 mmole) in a minimum of EtOAc. The degassed soln was irradiated using a medium pressure Hg vapour lamp with a quartz photolysis tube. After 24 hr the soln was evaporated *in vacuo* to give a residue which was chromatographed (grade III alumina, 35 g). Elution with benzene–$CHCl_3$ (3:1) and crystallisation from EtOAc gave **24** (58 mg, 30% overall yield) m.p. 184° (lit.[4,6] 184°, 189°) ν_{max} ($CHCl_3$) 1638, 1600, 1590 cm^{-1}; λ_{max} (EtOH); 358 (sh, 17,500), 348 (23,400), 235 (22,750), 264 (27,270), 244 (20,390), 225 nm (21,700); NMR ($CDCl_3$) δ 2.82 (t, 2H, J = 6 Hz); 3.82 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.23 (t, 2H, J = 6 Hz), 6.64 (s, H), 6.98 (d, H, J = 8.5 Hz), 7.03 (s, H), 7.24 (s, H), 8.09 (d, H, J = 8.5 Hz). (Found: C, 68.37; H, 5.81; N, 3.70. $C_{21}H_{21}NO_5$ requires: C, 68.65; H, 5.76; N, 3.81%).

Continued elution with benzene–$CHCl_3$ (2:1) afforded **17** (159 mg).

2,3,11,12-*Tetramethoxyprotoberberine hydroxide*, **25** (X = OH). Et_2O (500 ml) and conc HCl (6.75 ml) were added to a soln of **17** (1.2 g, 3.3 mmole) in MeOH (100 ml). The degassed soln was then irradiated as in the previous experiment. Removal of the solvent *in vacuo* gave a brown residue which was dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$ aq (2X), H_2O then dried (Na_2SO_4). Removal of the solvent gave a gum (1.2 g) which was chromatographed (grade III alumina, 100 g). Elution with benzene–EtOAc (3:1) gave **17** (726 mg).

Elution with EtOAc/MeOH (9:1) gave a gum (184 mg) which crystallised from $CHCl_3$–EtOAc to give **25** as yellow crystals (130 mg, 28% overall yield) m.p. 209–210°; ν_{max} ($CHCl_3$) 3400, 1628, 1600 cm^{-1}; λ_{max} (EtOH) 330 (15,540), 294 (15,920), 247 (14,200), 229 nm (ϵ 12,070), (alkaline soln) λ_{max} 357, 274, 223 nm; NMR ($CDCl_3$) δ 3.30 (t, 3H, J = 6 Hz), 4.02 (s, 3H), 4.07 (s, 3H), 4.13 (s, 3H), 4.18 (s, 3H), 5.26 (t, 2H, J = 6 Hz), 6.96 (s, H), 7.43 (s, H), 7.60 (d, H, J = 9 Hz), 8.42 (s, H), 8.63 (d, H, J = 9 Hz), 11.26 (br.s, H); *m/e* 352.1531 (P–OH, $C_{21}H_{22}NO_4$ requires: 352.1528), 338.1381 ($C_{20}H_{20}NO_4$ requires: 338.1392), 337.1312 ($C_{20}H_{19}NO_4$ requires 337.1313), 336.1251 ($C_{20}H_{18}NO_4$ requires: 336.1236), 322.1073 ($C_{19}H_{16}NO_4$ requires: 322.1079) 205.0739 ($C_{11}H_{11}NO_3$ requires: 205.0738).

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