REACTIONS OF 5-*BROMO*-2-*METHOXYTROPONE* AND 8-BROMO- AND 6,8-DIBROMOCYCLOHEPTA[b][1,4]BENZOXAZINES WITH o-AMINOPHENOL[1]

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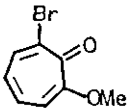
Abstract - Reaction of the title tropone (3) and 8-bromo compound (19) with o-aminophenol (4) in acetic acid affords the HBr salt of *8-(o-hydroxyanilino)cyclohepta[b][1,4]benzoxazine* (21) as the main product, whereas under basic conditions treatment of 19 with 4 results in the formation of mainly 2- and 3-formylphenoxazine. Reaction of 6,8-dibromo compound 20 with 4 produces various tropylium compounds having two annulated heterocycles. Possible reaction pathways involving unusual intramolecular transpositions of heterocycles are discussed.

It has been known that the nucleophilic reactivity of three isomeric bromomethoxytropones 1-3 is considerably different, and the displacement reaction on the methoxyl group at C-2 of 2 is expected to be retarded or slow due to the steric hindrance by the two neighboring groups.[2]



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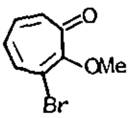

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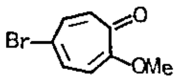

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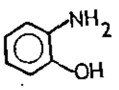

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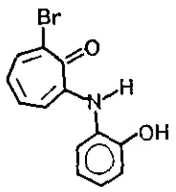

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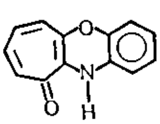
We have reported[3] that the reaction of 1 with o-aminophenol (4) affords mainly 2-bromo-7-(o-hydroxyanilino)tropone (5) besides a small amount of by-products (11 and 13, vide infra). On the other hand, the reaction between 2 and 4 was very complex and gave a wide variety of 1:1- (6 and 7) and 1:2-condensation products (8-13) besides the oxidative dimer 14.[4,5]



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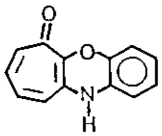

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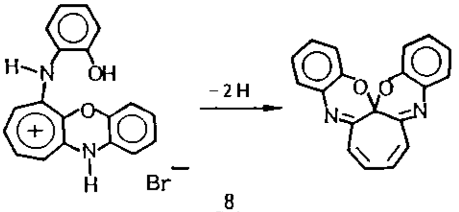

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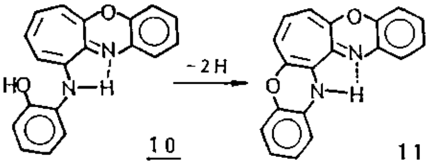

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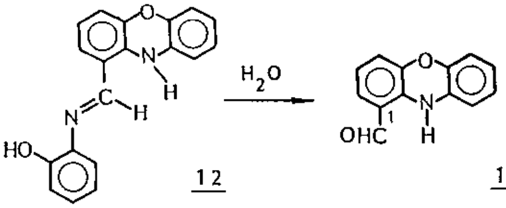

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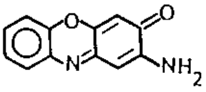
Meanwhile, it has become clear[6] that various 1:2-condensation products (8-13) are produced via intermediates 6-bromo- (15) and 10-bromocyclohepta[b][1,4]benzoxazine (16), which exist, in solution, in an equilibrium through an unprecedented intermolecular heterocycle-exchange reaction with a reagent 4. Moreover, we have



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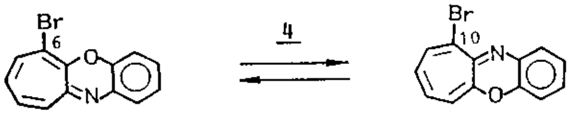

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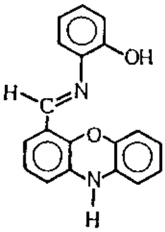
found[5] that the reaction of 15 with 4 easily affords all of these products (8-13) under suitable conditions, and the isomeric Schiff base 17 and its hydrolyzed product 18 are also produced under basic conditions.



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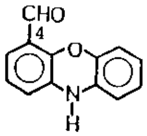

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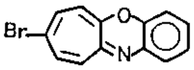
In this communication we wish to report our recent study on the reactions of 3, 8-bromo- (19), and 6,8-dibromocyclohepta[b][1,4]benzoxazine (20) with 4, which turns out to be also very complicated.



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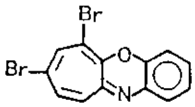

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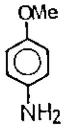

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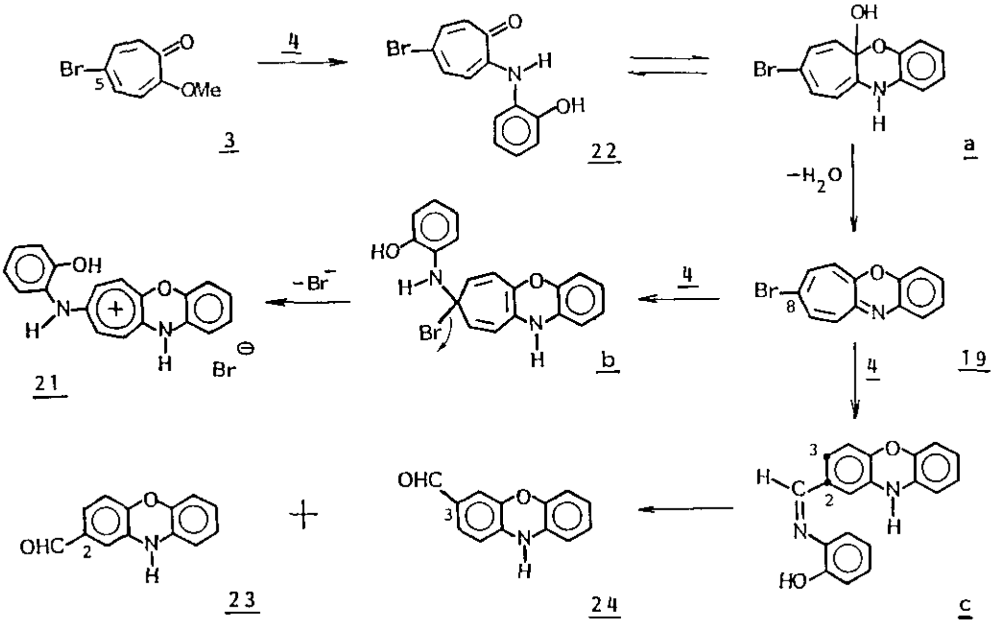
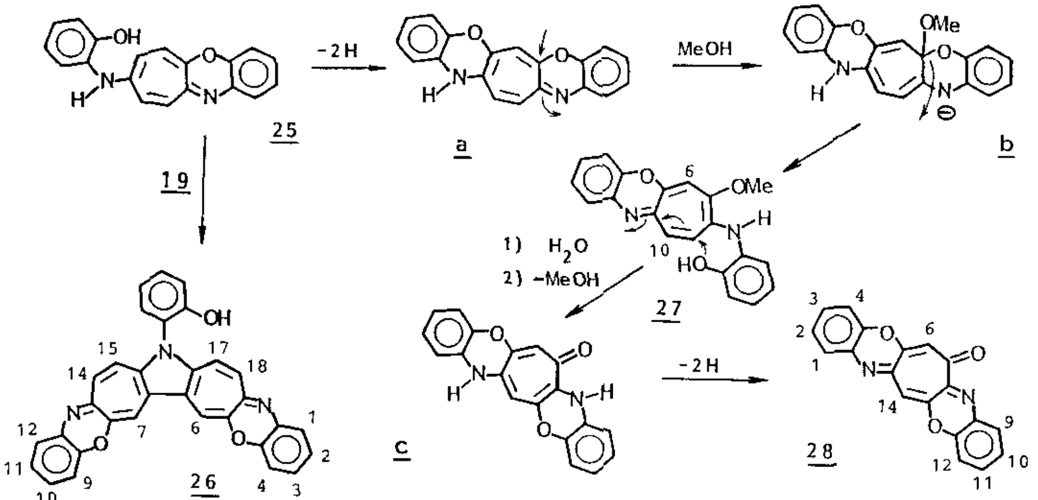
Heating of 3 with 4 in acetic acid for 2 h under reflux resulted in the formation of the HBr salt 21[7] (reddish brown needles, mp >300 °C, 75% yield), along with 19[8] (reddish brown needles, mp 163-164 °C, 8%) and 5-bromo-2-(o-hydroxyanilino)-tropone (22,[9] 5%). Treatment of 19 with 4 under the same reaction conditions gave 21 almost exclusively, while in butanol at 120 °C for 1h 21 was obtained in 90% yield besides trace amounts of 2-formyl- (23,[10] yellow needles, mp 219-221 °C) and 3-formylphenoxazine (24,[11] yellow needles, mp 170-171 °C). These products are apparently formed via unstable intermediates a and b and Schiff bases c (Scheme 1).

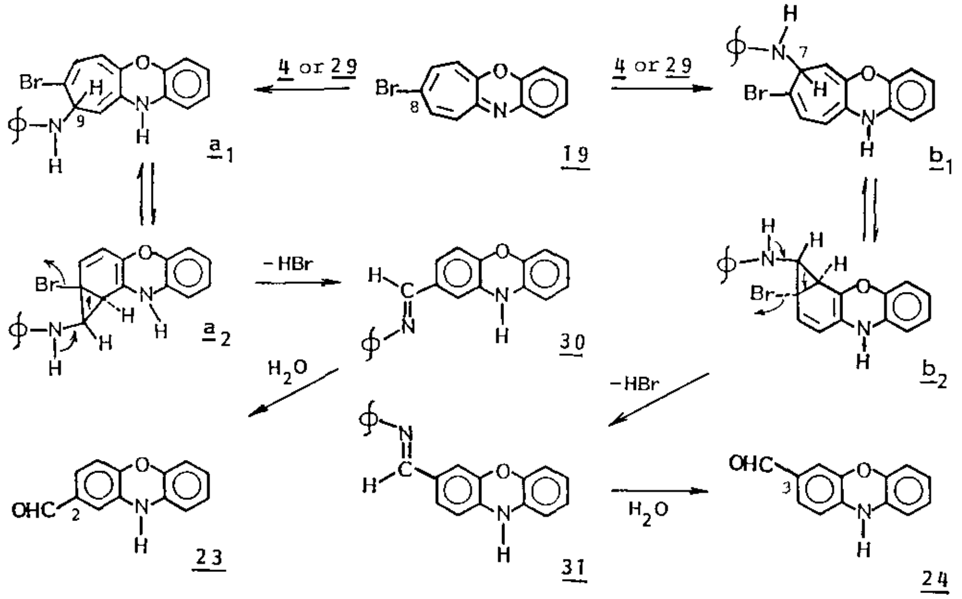


Scheme 1.

The free base 25 liberated from 21 by neutralization with DABCO was found to be very unstable but its structure was confirmed by the spectral data of the stable N,O-diacetyl derivative (25a,[12] brown needles, mp 115-117 °C). However, when a methanolic solution of 21 and DABCO (1:1) was allowed to stand at room temperature overnight, we obtained a mixture of 26[13] (15%, dark violet needles, mp >300 °C), 27[14] (≃10%, a yellow solid), and cyclohepta[1,2-b:4,5-b']di[1,4]benzoxazin-7-one (28,[15] 10%, reddish violet needles, mp 148-149 °C). Structures of these compounds were established on the basis of their respective spectral data taking into consideration the parameters of structurally related compounds such as 19 and 36 (see references). The pigment 26 is probably formed by the reaction of 25 with 19, followed by dehydrogenation, whereas 28 is obviously produced by an intramolecular transpositions of a heterocycle on the seven-membered ring



Scheme 2.

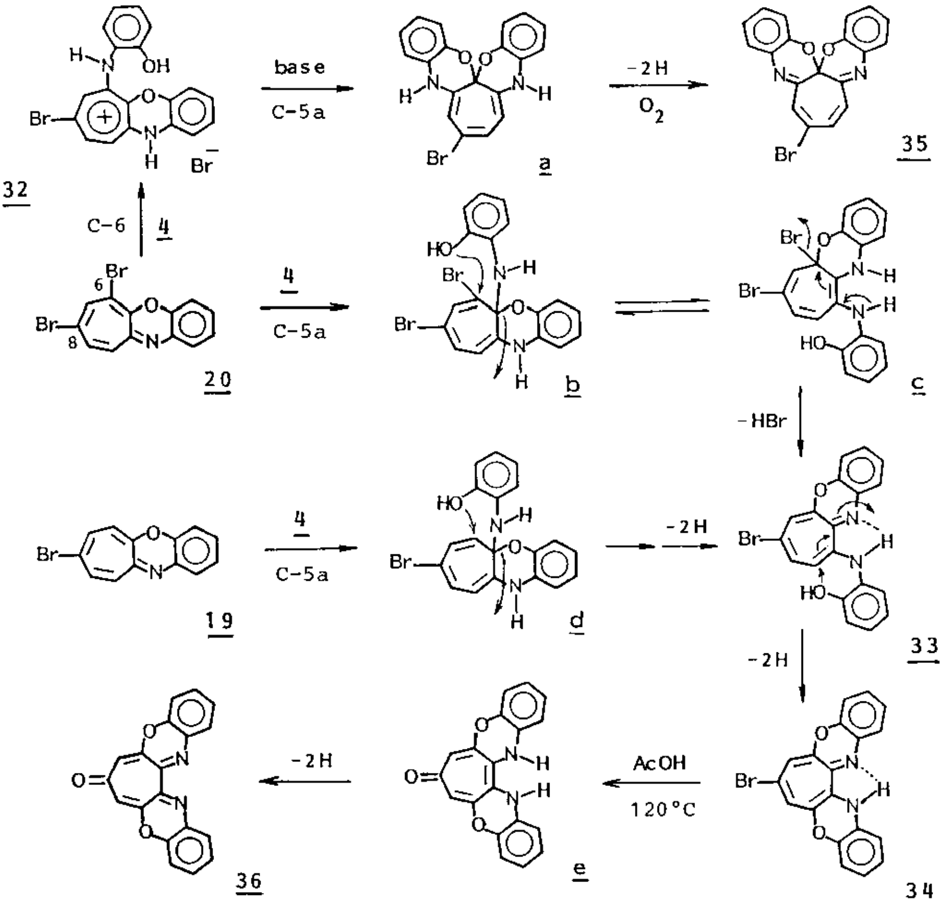


Scheme 3.

triggered by the initial attack of a solvent nucleophile (MeOH, H_2O etc.) at C-5a of 25 as illustrated in Scheme 2.

Treatment of 8-bromo compound 19 with 4 in refluxing butanol in the presence of 1 equiv. of DABCO gave 23 (33%), 24 (33%), 22 (15%), 33 (15%, vide infra), and 34 (3%, vide infra). When a butanolic solution of 19 and p-anisidine (29) was heated at 120 °C for 1h, a mixture of Schiff bases [30[16] (20%) and 31[17] (20%)] was obtained together with 23 (5%), 24 (5%), 22 (5%), and 33 (15%, vide infra). Possible pathways for the rearrangement products (from 19 with 4 or 29) are shown in Scheme 3.

Reaction of 20[18] (derived from 2,4-dibromo-7-methoxytropone and 4) with 4 (1:1.5) in acetic acid for 1.5 h under reflux afforded 32[19] (reddish brown needles, mp >300 °C, 40% yield) and 33[20] (dark brown needles, mp 191-193 °C, 45%), besides a small amount of ring-closed product 34[21] (dark violet needles, mp 256-257 °C).



Scheme 4.

Compounds 32 and 33 were easily cyclo-dehydrogenated on exposure to air to give the chiral acetal (13-bromocyclohepta[1,2-b:1,7-b']di[1,4]benzoxazine, 35,[22] 40%) and 7-bromocyclohepta[1,2-b:4,3-b']di[1,4]benzoxazine (34, 90%), respectively. When 34 was refluxed in acetic acid, p-tropoquinonoid compound 36[23] (reddish violet needles, mp >300 °C) was obtained having the symmetrical structure in an almost quantitative yield. Treatment of 19 with 4 also afforded 33 and 34 . Possible pathways for the formation of these products are illustrated in Scheme 4. It has been especially noted in the present study that only a slight change in the reaction conditions frequently caused quite different results in the product distributions. It is noteworthy that the transposition of the heterocycle takes place on the seven-membered nucleus also in the present series and resulting ring-closed compounds are easily dehydrogenated to give a fully conjugated system and a tropoquinonoid compound (see Scheme 4). Details of these results will be published elsewhere.

We are grateful to Professor Hiroshi Yamamoto (Okayama Univ.) for his helpful discussion.

REFERENCES AND NOTES

1. Partly presented at 45th National Meeting of the Chemical Society of Japan, Tokyo, 1980 (abstr. No. 4I03); 49th Meeting, Tokyo, 1984 (abstr. No. 2E06).
2. For general reviews on troponoid chemistry, see: T.Nozoe, "Non-benzenoid Aromatic Compounds", Ed. D.Ginsborg, Interscience, New York, 1959; pp. 339-433; T.Nozoe, K.Takase, H.Matsumura, T.Asao, K.Kikuchi, and S.Itô, "Daiyuki Kagaku (Comprehensive Organic Chemistry)", Ed. M.Kotake, 1960, Vol. 13, pp. 1-908, Asakura, Tokyo; F.Pietra, Chem. Rev., 1973, 73, 293-364; D.Lloyd, "Non-benzenoid Conjugated Carbocyclic Compounds", Elsevier, Amsterdam, 1984, pp. 1-431.
3. T.Nozoe, T.Someya, and H.Okai, Bull. Chem. Soc. Jpn., 1979, **52**, 1156.
4. T.Someya, H.Okai, H.Wakabayashi, and T.Nozoe, Bull. Chem. Soc. Jpn., 1983, **56**, 2756.
5. T.Nozoe, H.Okai, H.Wakabayashi, and S.Ishikawa, Bull. Chem. Soc. Jpn., submitted.
6. T.Nozoe, H.Okai, H.Wakabayashi, and S.Ishikawa, Chem. Lett., **1988**, 1589.
7. 21: Uv ($CHCl_3$) 274, 282, 320, 473nm, (MeOH + 6M NaOH) 275, 335, 467nm; ir (KBr) 3400 (NH) and 3200 cm^{-1} (OH); ms m/z 302 (M^+).
8. 19: Uv (MeOH) 262 (log ε 4.43), 271 (4.35), 298 (3.93), 414nm (4.12), (MeOH + 6M HCl) 265 (log ε 4.43), 273 (4.35), 325 (3.95), 447nm (4.06); ^1H nmr (270 MHz, $CDCl_3$) δ = 5.12 (1H, d, J=10.2 Hz, H-6), 5.84 (1H, d, J=13.2 Hz, H-10), 6.21 (1H, dd, J=13.2 and 2 Hz, H-9), 6.24 (1H, dd, J=10.2 and 2 Hz,

H-7), 6.38 (1H, m, H-4), 6.7-6.8 (3H, m, H-1,2,3); ^{13}C nmr (67.8 MHz, CDCl$_3$) δ = 111.4 (d), 114.3 (d), 121.9 (s), 124.8 (d), 126.4 (d), 128.0 (d), 135.1 (d), 135.4 (s), 136.1 (d), 139.7 (d), 146.8 (s), 157.0 (s), 158.9 (s); ms m/z 275 (M$^+$, 99%), 273 (M$^+$, 100%). Anal. Calcd for $C_{13}H_8NOBr$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.92; H, 3.22; N, 5.13.

9. 22: Uv (MeOH) 237 (log ε 4.36), 353 (4.16), 422nm (4.16), (MeOH + 6M NaOH) 229 (log ε 4.43), 355 (3.98), 431nm (4.13); ir (KBr) 3290 (NH) and 3275 cm^{-1} (OH); ^{1}H nmr (270 MHz, CD$_3$OD) δ = 6.84 (1H, d, J=11.5 Hz, H-3), 6.93 (1H, td, J=8 and 2 Hz, H-5'), 6.97 (1H, dd, J=8 and 2 Hz, H-3'), 7.01 (1H, d, J=12.4 Hz, H-7), 7.15 (1H, td, J=8 and 2 Hz, H-4'), 7.32 (1H, dd, J=8 and 2 Hz, H-6'), 7.59 (1H, dd, J=11.5 and 2 Hz, H-4), 7.66 (1H, dd, J=12.4 and 2 Hz, H-6); ms m/z 293 (M$^+$, 98%), 291 (M$^+$, 100%). Anal. Calcd for $C_{13}H_{10}NO_2Br$: C, 53.45; H, 3.45; N, 4.80. Found: C, 53.31; H, 3.54; N, 4.69.
10. 23: Uv (MeOH) 225 (log ε 4.29), 272 (4.42), 324 (3.95), 400nm (3.47); ir (KBr) 3380 (NH), 1677 cm^{-1} (C=O); ^{1}H nmr (100 MHz, acetone-d$_6$) δ = 6.52 (1H, m, H-6), 6.67 (1H, d, J=8.3 Hz, H-4), 6.57-6.82 (3H, m, H-7,8,9), 6.96 (1H, d, J=2 Hz, H-1), 7.22 (1H, dd, J=8.3 and 2 Hz, H-3), 7.63 (1H, br, NH), 9.74 (1H, s, CHO). Found: m/z 211.0668. Calcd for $C_{13}H_9NO_2$: M, 211.0667.
11. 24: Uv (MeOH) 226 (log ε 4.27), 270 (4.22), 308 (3.67), 400nm (4.08); ir (KBr) 3340 (NH) and 1662 cm^{-1} (C=O); ^{1}H nmr (100 MHz, acetone-d$_6$) δ = 6.51-6.78 (4H, m, H-6,7,8,9), 6.68 (1H, d, J=8.3 Hz, H-1), 7.05 (1H, d, J=2 Hz, H-4), 7.32 (1H, dd, J=8.3 and 2 Hz, H-2), 8.01 (1H, br, NH), 9.66 (1H, s, CHO). Found: m/z 211.0656. Calcd for $C_{13}H_9NO_2$: M, 211.0667.
12. 25a: Uv (MeOH) 215 (log ε 4.45), 261 (4.47), 270 (4.43), 306 (3.99), 320^{sh} (3.91), 333 (3.73), 421nm (4.18), (MeOH + 6M HCl) 221 (log ε 4.41), 266 (4.47), 273 (4.52), 325 (4.04), 457 (4,12) 474nm^{sh} (4.12); ir (CHCl$_3$), 1770 and 1670 cm^{-1} (C=O); ^{1}H nmr (270 MHz, CDCl$_3$) δ = 1.95 (3H, br, AcN), 2.31 (3H, s, AcO), 5.23 (1H, d, J=10.3 Hz, H-6), 5.55 (1H, dd, J=10.3 and 1 Hz, H-7), 6.05 (1H, d, J=13.2 Hz, H-10), 6.14 (1H, dd, J=13.2 and 1 Hz, H-9), 6.37 (1H, m, H-4), 6.7-7.5 (7H, m, H-1,2,3,3',4',5',6'). Found: m/z 386.1237. Calcd for $C_{23}H_{18}N_2O_4$: M, 386.1267.
13. 26: Uv (MeOH) 242 (log ε 4.15), 280 (4.22), 336 (4.32), 430 (4.00), 448 (3.99), 486^{sh} (3.86), 520^{sh} (3.88), 550 (3.95), 590 (3.80), 650nm^{sh} (3.32), (MeOH + 6M HCl) 252 (log ε 4.28), 284 (4.12), 360 (4.45), 486 (3.86), 515^{sh} (3.84), 594 (4.00), 630nm^{sh} (3.98); ^{1}H nmr (270 MHz, DMSO-d$_6$) δ = 5.98 (2H, d, J=12.5Hz, H-6,10), 6.07 (2H, d, J=12.5 Hz, H-7,9), 6.29 (2H, s, H-17,18), 6.51 (2H, dd, J=8 and 2 Hz, H-4,12), 6.72-6.92 (7H, m, H-1,2,3,13,14,15,5'), 7.04 (1H, dd, J=8 and 2 Hz, H-3'), 7.19 (1H, dd, J=8 and 2 Hz, H-6'), 7.36 (1H, td, J=8 and 2 Hz, H-4'); ms m/z 439 (M$^+$, 100%).
14. 27: Uv (MeOH) 243, 332, 430nm; ^{1}H nmr (270 MHz, CDCl$_3$) δ = 3.28 (3H, s, OMe), 5.89 (1H, s, H-6), 6.84 (1H, d, J=13.2 Hz, H-10), 6.92 (1H, d, J=13.2 Hz, H-9), 6.9-7.5 (10H, m, other H); ms m/z 330 (M$^+$).
15. 28: Uv (MeOH) 262 (log ε 4.36), 344 (4.02), 508nm (4.27); ^{1}H nmr (270 MHz, CDCl$_3$) δ = 6.60 (1H, s, H-14), 6.63 (1H, s, H-6), 7.01 (1H, dd, J=8 and 2 Hz, H-12), 7.15 (1H, td, J=8 and 2 Hz, H-10), 7.17 (1H, dd, J=8 and 2 Hz, H-4),

7.25 (1H, m, H-2), 7.35 (1H, m, H-11), 7.38 (1H, m, H-3), 7.56 (1H, m, H-9), 7.71 (1H, m, H-1). Found: m/z 314.0661. Calcd for $C_{19}H_{10}N_2O_3$: M, 314.0692.

16. 30: Uv (MeOH) 227 (log ε 4.40), 278 (4.45), 324 (4.34), 387nm (3.83); ir (KBr) 3400 cm^{-1} (NH); ^{1}H nmr (100 MHz, acetone-d_6) δ =3.81 (3H, s, OMe), 6.5-6.8 (5H, m, H-4,6,7,8,9), 6.8-7.3 (6H, m, H-1,3,2',3',5',6'), 7.51 (1H, br, NH), 8.37(1H, s, HC=N). Found: m/z 316.1213. Calcd for $C_{20}H_{16}N_2O_2$: M, 316.1212.
17. 31: Uv (MeOH) 231 (log ε 4.35), 264 (4.23), 317 (3.97), 403nm (4.34); ir (KBr) 3425 cm^{-1} (NH); ^{1}H nmr (100 MHz, acetone-d_6) δ = 3.81 (3H, s, OMe), 6.5-6.8 (5H, m, H-1,6,7,8,9), 6.9-7.3 (6H, m, H-2,4,2',3',5',6'), 7.76 (1H, br, NH), 8.36(1H, s, HC=N). Found: m/z 316.1204. Calcd for $C_{20}H_{16}N_2O_2$: M, 316.1212.
18. 20: dark brown needles, mp 165-166 °C; uv (MeOH) 234 (log ε 4.29), 261 (4.42), 270 (4.38), 313 (3.95), 325^{sh} (3.88), 414nm (4.12), (MeOH + 6M HCl) 238 (log ε 4.21), 265 (4.45), 273 (4.47), 324 (4.00), 452 (4.05), 473nm^{sh} (4.03); ^{1}H nmr (270 MHz, $CDCl_3$) δ =5.89 (1H, d, J=12.9 Hz, H-10), 6.19 (1H, dd, J=12.9 and 2.2 Hz, H-9), 6.60 (1H, m, H-4), 6.79 (1H, d, J=2.2 Hz, H-7), 6.8-6.9 (3H, m, H-1,2,3); ^{13}C nmr (67.8 MHz, $CDCl_3$) δ = 109.8 (s), 114.8 (d), 120.1 (s), 125.4 (d), 126.6 (d), 128.6 (d), 135.1 (s), 136.5 (d), 138.2 (d), 139.5 (d), 146.4 (s), 152.5 (s), 155.6 (s); ms m/z 355 (M^+, 50%), 353 (M^+, 100%), 351 (M^+, 51%). Anal. Calcd for $C_{13}H_7NOBr_2$: C, 44.23; H, 2.00; N, 3.97. Found: C, 44.43; H, 2.13; N, 3.77.
19. 32: Uv (MeOH) 274, 315, 462nm, (MeOH + 6M NaOH) 274, 335, 470, 500nm^{sh}; ms m/z 382 (M^+), 380 (M^+).
20. 33: Uv (MeOH) 236 (log ε 4.15), 270 (4.30), 320 (3.70) 450-480nm (3.61), (MeOH + 6M HCl) 231 (log ε 4.05), 272 (4.56), 314 (3.81), 466nm (3.60), (MeOH + 6M NaOH) 269 (log ε 4.21), 494nm (3.65); ir (KBr) 3400 cm^{-1} (OH); ^{1}H nmr (100 MHz, acetone-d_6) δ = 6.02 (1H, d, J=10.8 Hz, H-9), 6.22 (1H, d, J=2 Hz, H-6), 6.55 (1H, dd, J=10.8 and 2Hz, H-8), 6.83-7.29 (8H, m, H-1,2,3,4,3',4',5',6'), 8.63 (2H, br, NH,OH); ms m/z 382 (M^+), 380 (M^+).
21. 34: Uv ($CHCl_3$) 262 (log ε 4.38), 432 (3.83), 490 (3.89), 525 (3.92), 568nm (3.83), ir (KBr) 3290 cm^{-1} (NH); ^{1}H nmr (270 MHz, $CDCl_3$) δ = 6.47 (2H, m, H-4,10), 6.62-6.80 (6H, m, H-1,2,3,11,12,13), 7,36 (2H, s, H-6,8), 7.50 (1H, br, NH); ms m/z 380 (M^+), 378 (M^+).
22. 35: Uv (MeOH) 231 (log ε 4.28), 291 (4.31), 375nm (3.85); ^{1}H nmr (270 MHz, $CDCl_3$) δ = 6.70 (1H, dd, J=12.5 and 1.5 Hz, H-14), 6.73 (2H, m, H-4,7), 6.85 (1H, d, J=12.5 Hz, H-15), 7.21 (4H, m, H-2,3,8,9), 7.44 (1H, d, J=1.5 Hz, H-12), 7.67 (2H, m, H-1,10); ms m/z 380 (M^+), 378 (M^+).
23. 36: Uv (MeOH) 238 (log ε 4.34), 285 (4.18), 354 (3.91) 505nm (4.00), (MeOH + 6M HCl) 276 (log ε 4.46), 385 (4.02), 488^{sh} (3.93), 522nm (4.01); ^{1}H nmr (270 MHz, $CDCl_3$) δ = 6.23 (2H, s, H-6,8), 7.11 (2H, dd, J=8 and 2 Hz, H-4,10), 7.21 (2H, td, J=8 and 2 Hz, H-2,12), 7.41 (2H, td, J=8 and 2 Hz, H-3,11), 7.79 (2H, dd, J=8 and 2 Hz, H-1,13); ^{13}C nmr (67.8MHz, $CDCl_3$) δ = 113.9 (d), 115.3 (d), 124.8 (d), 130.6 (d), 133.1 (d), 133.7 (s), 145.8 (s), 147.8 (s), 150.1 (s), 182.9 (s). Found: m/z 314.0690. Calcd for $C_{19}H_{10}N_2O_3$: M, 314.0690.

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