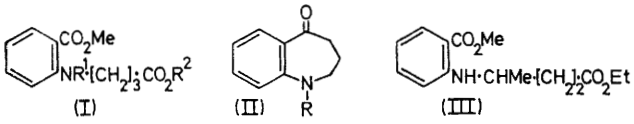
Reactions of Methyl Anthranilate with Ethyl γ-Bromobutyrate

By (Miss) I. McCall, G. R. Proctor,* and L. Purdie, Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow C.1

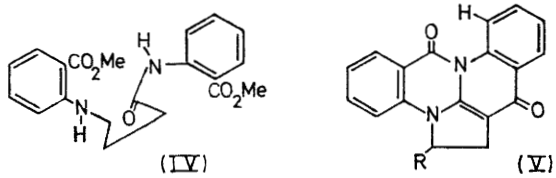
When methyl anthranilate and ethyl γ-bromobutyrate are heated together, various products are formed: above 125° the main product is a yellow compound for which a 7b,12b-diazabenz[*e*]aceanthrylene structure is postulated.

MONO-*N*-alkylation of anthranilates is a straightforward reaction [1] whereas, probably owing to hydrogen bonding,[2a] replacement of the second amino-hydrogen atom is difficult and di-*N*-alkylanthranilates are rare.[2] Astill and Boekelheide [3] have, however, prepared the compound (I; $R^1 = R^2 = Me$) by sequential alkylation of methyl anthranilate with methyl γ-bromobutyrate [yielding (I; $R^1 = H$, $R^2 = Me$)] and with methyl iodide. Dieckmann cyclisation of (I; R^1 = tosyl, R^2 = Et) gave (II; R = tosyl).[4] In the latter case, it was convenient to prepare the diester (I; R^1 = tosyl, R^2 = Et) by reaction of methyl *N*-tosylanthranilate with ethyl γ-bromobutyrate;[4] this process has recently been improved (see Experimental section).

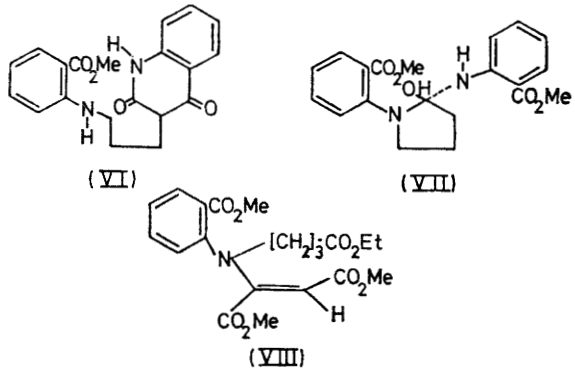


As the reaction of methyl *N*-tosylanthranilate with ethyl γ-bromovalerate was initially unsuccessful,[5] we tried the reaction of methyl anthranilate with ethyl γ-bromovalerate: at 100° none of the expected diester (III) was obtained, and at 140° the main product was a yellow solid ($C_{19}H_{14}N_2O_2$).[5] This observation led to a re-examination of the reaction between methyl anthranilate and ethyl γ-bromobutyrate. We found that this proceeded at 80—100°; after distillation of the product (I; $R^1 = H$, $R^2 = Et$) a small yellow solid residue ($C_{18}H_{12}N_2O_2$) * remained. At higher temperatures (>125°) the yield of (I; $R^1 = H$, $R^2 = Et$) diminished, that of the yellow solid slightly increased, and several other products appeared. The volatile fraction was shown to consist mainly of *NN*-dimethylaniline and methyl *N*-methylanthranilate:[1] the residue also contained a substance, m.p. 88° ($C_{20}H_{22}N_2O_5$), which has been shown to have structure (IV) (see Experimental section).

Separate experiments confirmed that methyl anthranilate and the diester (I; $R^1 = H$, $R^2 = Et$) when heated together gave the compound (IV), and that the latter when heated with hydrogen bromide to 170° gave the yellow compound ($C_{18}H_{12}N_2O_2$) previously described. Implication of the amide (IV) as an intermediate limits the number of structural possibilities for the yellow solid: the most probable of these is (V; R = H) particularly since the n.m.r. spectrum reveals a signal at τ 0·5. Such deshielding is diagnostic of protons lying in the cone of a carbonyl group.[6]



Degradative evidence for the structure (V; R = H) was hard to obtain; bromination, oxidation, reaction with hydrogen bromide, and reaction with methyl iodide yielded no useful results. The amide group in (V; R = H) was reversibly cleaved (*cf.* ref. 3) by dilute sodium hydroxide, and reaction with sodium borohydride gave a colourless substance ($C_{18}H_{14}N_2O_3$) of unknown structure. Thus while the structure of compound (V; R = H) remains unconfirmed, it has been demonstrated to arise from (I; R = H) *via* (IV).



The compound ($C_{19}H_{14}N_2O_2$) [5] from ethyl γ-bromovalerate closely resembles the yellow compound ($C_{18}H_{12}N_2O_2$) and has been tentatively formulated as (V; R = Me).

This work re-emphasises the poor nucleophilicity of the amino-group in compounds such as (I; $R^1 = H$, $R^2 = Et$); thus we find that reaction with toluene-*p*-sulphonyl chloride in pyridine only proceeds at *ca.* 90°, giving indifferent yields of (I; R^1 = tosyl, $R^2 = Et$), and reaction of (I; $R^1 = H$, $R^2 = Et$) with 2-chloro-3-iodopropene (under conditions found successful for

* This appears to be the same as one arising when methyl anthranilate is heated with γ-butyrolactone.[3]

[1] J. Houben and W. Brassert, *Ber.*, 1906, **39**, 3233.

[2] (*a*) E. Uhlig and K. Doering, *Chem. Ber.*, 1964, **97**, 1127; (*b*) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 1953, 2386.

[3] D. B. Astill and V. Boekelheide, *J. Amer. Chem. Soc.*, 1955, **77**, 4079.

[4] G. R. Proctor, *J. Chem. Soc.*, 1961, 3989.

[5] W. Peaston, Ph.D. Thesis, University of Strathclyde, Glasgow, 1968.

[6] (*a*) A. M. Khan, G. R. Proctor, and L. Rees, *J. Chem. Soc.* (*C*), 1966, 990; (*b*) E. C. Taylor and Y. Shvo, *J. Org. Chem.*, 1968, **33**, 1719.

methyl iodide [3]) was unsuccessful. On the other hand alkylation does take place when (I; R^1 = H, R^2 = Et) is heated with dimethyl acetylenedicarboxylate; [7] however the yield is poor, and as the product is a gum one cannot say with certainty whether it is exclusively the *trans*-isomer (VIII) or contains some of the *cis*-isomer.[7,8]

EXPERIMENTAL

Ethyl γ-N-(o-Methoxycarbonylphenyl)-p-tolylsulphonamidobutyrate (I; R^1 = tosyl, R^2 = Et).[4]—(*a*) Ethyl 4-(*o*-methoxycarbonylanilino)butyrate (I; R^1 = H, R^2 = Et) (104 g.), toluene-*p*-sulphonyl chloride (76 g.), and dry pyridine (1 l.) were heated together for 12 hr. on a steam-bath. The cooled mixture was poured into an excess of ice–concentrated hydrochloric acid, and the precipitated product was crystallised from ethanol; yield 65 g., m.p. 98—100° (*cf.* ref. 4).

(*b*) Methyl *p*-tolylsulphonylanthranilate (230 g.) in anhydrous dimethylformamide (600 ml.) was slowly treated with sodium hydride (50% dispersion, 48 g.) with stirring under nitrogen during 1 hr. After a further 2 hr., ethyl γ-bromobutyrate [9] (170 g.) was added, and 12 hr. later the temperature was raised to 90° during 90 min. and maintained there for 6 hr. Methanol–benzene was cautiously added to the cooled mixture, which was then poured into an excess of water and extracted with benzene. The product was obtained (300 g.) as usual; it could be used without further purification.

2,3-Dihydro-1-p-tolylsulphonyl-1-benzazepin-5(4H)-one (II; R = tosyl).[4]—Methyl *p*-tolylsulphonylanthranilate (58 g.), ethyl γ-bromobutyrate (50 g.), and sodium hydride (50% dispersion; 12 g.) reacted together in dry dimethylformamide (500 ml.) as described in the previous paragraph. After the reaction was complete, sodium hydride (50% dispersion; 12 g.) was added slowly, followed by methanol (0·5 ml.) in benzene (20 ml.). The mixture was stirred at 20° for 24 hr. and at 100° for 2 hr., then poured into excess of ice–dilute hydrochloric acid; extraction with chloroform yielded ethyl 2,3,4,5-tetrahydro-5-oxo-1-*p*-tolylsulphonyl-1-benzazepine-4-carboxylate [4] (74 g.), which was hydrolysed by the published [4] method to give the product (47 g.), m.p. 126°.

Ethyl γ-Bromovalerate.—The literature method [9] for ethyl γ-bromobutyrate was applied to γ-valerolactone (200 g.; commercial sample); the product (272 g., 65%) had b.p. 104°/2 mm. (Found: C, 40·65; H, 6·3; Br, 38·1. $C_7H_{13}BrO_2$ requires C, 40·2; H, 6·25; Br, 38·25%), $\nu_{max.}$ (film) 1727 cm.$^{-1}$ (ester C=O), τ 5·5—6·2 [m, C(4)–H and MeCH_2], 7·2—8·3 (m, 2- and 3-H_2), 8·27 (d, 5-H_3), and 8·75 (t, *Me*CH_2).

1,2-Dihydro-1-methyl-7b,12b-diazabenz[e]aceanthrylene-3,8-dione (V; R = Me) (with W. Peaston).—Methyl anthranilate (40 g.) and ethyl γ-bromovalerate (25 g.) were heated for 8 hr. at 140°. The mixture was cooled, poured into excess of dilute sodium hydrogen carbonate solution, and extracted with chloroform. The solvent was removed and after distillation at 120°/0·1 mm., the residue crystallised in yellow prisms, m.p. 208° (29 g.), from ethanol [Found: C, 75·35; H, 4·85; N, 9·25%; *M* (mass spectrum), 302·10552. $C_{19}H_{14}N_2O_2$ requires C, 75·55; H, 4·65; N, 9·3%; *M*, 302·10532], $\nu_{max.}$ (Nujol) 1709, 1630, 1600, and 1585 cm.$^{-1}$ (various C=O and C=C), τ ($CDCl_3$) 0·62 and 0·75 (dd, aryl H in *peri*-position), 1·6—3·2 (m, 7 aryl H), 5·3 (m, 11-H), 6·3—7·4 (m, 10-H_2), and 8·6 (d, Me).

Reactions of Methyl Anthranilate with Ethyl γ-Bromobutyrate (*cf.* ref. 3).—(*a*) Methyl anthranilate (192 g.) and ethyl γ-bromobutyrate (96 g.) were heated together at 80—85° for 24 hr. The product was cooled, treated with excess of dilute sodium hydrogen carbonate solution and extracted with ether, then fractionated to give methyl anthranilate, b.p. 60—110°/0·05 mm., and *ethyl 4-(o-methoxycarbonylanilino)butyrate* (I; R^1 = H, R^2 = Et) (104 g.), b.p. 130—150°/0·05 mm., m.p. 46° (Found: C, 63·3; H, 7·1; N, 5·4. $C_{13}H_{19}NO_4$ requires C, 63·45; H, 7·25; N, 5·3%), $\nu_{max.}$ (film) 3400 (NH), and 1740 and 1688 (ester) cm.$^{-1}$, τ 1·9—3·5 (4H, several m, aryl), 2·1br (s, NH exchangeable), 5·83 (2H, q), 6·12 (3H, s), 6·5—6·9 (2H, m), 7·4—8·2 (4H m), and 8·75 (3H, t).

On hydrolysis with aqueous ethanolic sodium hydroxide, the diester (6 g.) gave the corresponding *diacid* (4 g.), m.p. 192° (efferv.) (Found: C, 59·35; H, 5·9; N, 6·6. $C_{11}H_{13}NO_4$ requires C, 59·25; H, 5·9; N, 6·3%).

The residue from the fractionation consisted of two products, m.p. 88 and 299° (see later).

(*b*) When reaction (*a*) was repeated at 110—115°; distillation yielded methyl anthranilate as before, but contaminated with *NN*-dimethylaniline and methyl *N*-methylanthranilate (see later), followed by ethyl 4-(*o*-methoxycarbonylanilino)butyrate (75 g.). The residue was crystallised from light petroleum (b.p. 60—80°) yielding *4-(o-methoxycarbonylanilino)-N-(o-methoxycarbonylphenyl)butyramide* (IV) (15 g.), m.p. 88° [Found: C, 64·65; H, 5·95; N, 7·25%; *M* (osmometry), 371. $C_{20}H_{22}N_2O_5$ requires C, 64·85; H, 6·0; N, 7·55%; *M*, 370], $\nu_{max.}$ (Nujol) 3310 (NH), 1700 (C=O), and 1675 (C=O) cm.$^{-1}$, τ ($CDCl_3$) −1·15br (s, NH), 1·12—3·5 (m, 8 aryl H and NH), 6·08(s) and 6·15(s) (2 × Me), 6·4—6·8 (m, CH_2), and 7·2—8·0 (m, 2 × CH_2). Addition of deuterium oxide caused the signal at τ — 1·15 to disappear, but it was not clear whether the signals between τ 1·85 and 3·5 changed significantly. [Alkaline hydrolysis yielded anthranilic acid and 4-(*o*-carboxyanilino)-butyric acid, m.p. 192° (efferv.)]. The insoluble residue gave a compound, m.p. 299° (see later).

(*c*) When experiment (*a*) was repeated at 140°, distillation yielded firstly methyl anthranilate, *NN*-dimethylaniline and methyl *N*-methylanthranilate. These were separated by a combination of fractional distillation and column chromatography on silica gel MFC. *NN*-Dimethylaniline was identical with a commercial sample and methyl *N*-methylanthranilate [1] was made for comparison by heating methyl anthranilate with methyl iodide at 40°C (Found: N, 8·45. Calc. for $C_9H_{11}NO_2$; N, 8·5%), $\nu_{max.}$ (film) 3300 (NH) and 1680 (C=O) cm.$^{-1}$, τ ($CDCl_3$) 7·14 (d, Me; collapsed to a singlet on addition of deuterium oxide).

The second fraction, as before, was ethyl 4-(*o*-methoxycarbonylanilino)butyrate (30 g.); the residue was crystallised from ethanol yielding a yellow powder, m.p. 299° (2·5 g.): this was *1,2-dihydro-7b,12b-diazabenz[e]aceanthrylene-3,8-dione* (*cf.* ref. 3) (Found: C, 75·5; H, 4·6; N, 9·85. $C_{18}H_{12}N_2O_2$ requires C, 75·0; H, 4·2; N, 9·7%), $\nu_{max.}$ (Nujol) 1710 (C=O), 1630 (C=O or C=C), and 1585 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 224, 243, 264, 305, and 347 nm. (ε 15,510, 18,280, 10,410, 7406, and 16,650), τ ($CDCl_3$) 0·5 (m, aryl H in *peri*-position), 1·5—3·2 (m, 7 aryl H), 5·7 (t, CH_2), and 6·7 (t, CH_2).

(*d*) Methyl anthranilate and ethyl γ-bromobutyrate were

[7] E. Winterfeldt, *Angew. Chem. Internat. Edn.*, 1967, 423.
[8] S. K. Khetan and M. U. George, *Tetrahedron*, 1969, **25**, 527.
[9] J. Lavety and G. R. Proctor, *Org. Synth.*, 1965, 45.

heated together at 185°; small quantities of all the foregoing products were identified along with N-*phenyl*-2-*pyrrolidone* (22 g.), b.p. 120°/0·1 mm., needles, m.p. 67—68° [*from* light petroleum (b.p. 60—80°)] (lit.,[3] 70—71°), identical with material previously obtained,[10] τ ($CDCl_3$) 2·15—2·95 (5 aryl H), 6·11 (t, 3-H_2), and 7·2—8·1 (m, 2 × CH_2). *N*-Phenyl-2-pyrrolidone was also obtained when ethyl 4-(*o*-methoxycarbonylanilino)butyrate was heated to 200°.

Reaction of Ethyl 4-(o-*Methoxycarbonylanilino*)*butyrate with Methyl Anthranilate.*—When equimolar proportions of these esters were heated together at 185° for 12 hr., work-up as before yielded an oil from which the starting materials were distilled (*ca.* 50%). The residue was extracted with ethanol, from which the diazabenzaceanthrylene (V; R = H) (*ca.* 8%) crystallised as before, m.p. 299°. From the mother liquor 4-(*o*-methoxycarbonylanilino)-*N*-(*o*-methoxycarbonylphenyl)butyramide (IV) (*ca.* 10%), m.p. 88°, was obtained. When the latter compound (2 g.) was saturated with gaseous hydrogen bromide and heated for 20 hr. at 140°, the diazabenzaceanthrylene (V; R = H) (600 mg.) was obtained, m.p. 299°.

Reactions of 1,2-*Dihydro*-7b,12b-*diazabenz*[e]*aceanthrylene*-3,8-*dione* (V; R = H).—(*a*) Passage of gaseous hydrogen bromide into a chloroform solution of the title compound yielded a white solid, m.p. >340°, which was insoluble in all solvents but which reverted to the starting material on contact with water.

(*b*) When the title compound in chloroform was treated with bromine in chloroform, amorphous brown materials were obtained.

(*c*) The title compound was recovered after hydrogenation in either ethanol or glacial acetic acid over platinic oxide or palladised charcoal (10%) at pressures up to 50 lb. $in.^{-2}$.

(*d*) Excess of methyl iodide in refluxing acetone had no effect on the title compound.

(*e*) The title compound dissolved in warm ethanolic aqueous sodium hydroxide solution (10%) giving a green solution which on neutralisation with dilute hydrochloric acid solution gave a white amorphous powder, m.p. 290° (decomp.). The latter was refluxed with ethanol containing concentrated sulphuric acid (a few drops) to give the starting material, m.p. 299°.

(*f*) The title compound (400 mg.) in ethanol (100 ml.) and benzene (25 ml.) was stirred for 24 hr. with sodium borohydride (1 g.). After dilution with water, removal of benzene, and neutralisation of the aqueous layer, the product (390 mg.) was obtained by extraction with chloroform. It crystallised from chloroform to yield a colourless *solid*, m.p. 161—162° (Found: C, 70·8; H, 4·65; N, 9·4. $C_{18}H_{14}N_2O_3$ requires C, 70·65; H, 4·6; N, 9·15%), $\nu_{max.}$ (Nujol) 1628 $cm.^{-1}$.

2-*Chloro*-3-*iodopropene.*—Commercially available 2,3-dichloropropene in acetone was treated with an equimolar proportion of sodium iodide in acetone; sodium chloride was filtered off and evaporation left the crude product, which was used without further purification.

Ethyl N-(1,2-*Bismethoxycarbonylvinyl*)-4-(o-*methoxycarbonylanilino*)*butyrate* (VIII).—Ethyl 4-(*o*-methoxycarbonylanilino)butyrate (I; R^1 = H, R^2 = Et) (5·3 g.), dimethyl acetylenedicarboxylate (3 ml.), and dry toluene (80 ml.) were refluxed together for 72 hr. Chromatography on silica gel MFC and elution with benzene–ether (94 : 6) gave the *product* (2·8 g.) as a gum, b.p. 180°/0·5 mm. (Found: C, 59·3; H, 6·8; N, 3·5. $C_{20}H_{25}NO_8$ requires C, 59·0; H, 6·3; N, 3·45%), $\nu_{max.}$ (film) 1738, 1725, and 1695 (ester C=O) $cm.^{-1}$, τ ($CDCl_3$) 1·75—2·7 (m, 4 aryl H), 5·25 (s, 1 olefinic H), 5·6—6·6 (m, 2 × CH_2), 6·02, 6·27, and 6·3 (each s, Me), 7·5—8·2 (m, 2 × CH_2), and 8·75 (t, Me).

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[10] G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 1957, 2302 and 2312.