421. p-*Arsanilic Acid Derivatives of* N-*Substituted Malonamides.*

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A STUDY has been made of compounds of the type

(*p*) $H_2O_3As{\cdot}C_6H_4{\cdot}NH{\cdot}CH(CO{\cdot}NHR)_2$ (I),

of which one (R = H) has been previously described (Lewis and Bent, *J. Amer. Chem. Soc.*, 1926, **48**, 949). They are made by condensing the appropriate bromomalonamide with *p*-arsanilic acid. Some bromomalonalkylamides were also prepared, but could not be condensed with *p*-arsanilic acid.

In physiological tests the compound having R = H was found curative in large doses. Of the homologues, only the bisethylamide showed slight therapeutic effect, and with increasing length of R the toxicity gradually increased.

p-*Arsonoanilinomalonamide* (I; R = H). Arsanilic acid (1·74 g.) in *N*-NaOH (7·75 c.c.) and bromomalonamide (Backes, West, and Whiteley, J., 1921, **119**, 359) (2·8 g.) were boiled for 2—3 hr. under reflux until a bulky ppt. had separated. The time varies considerably with different p_H of the solution. The ppt. was purified by repeated solution in the minimum amount of cold *N*-NaOH and repptn. by dil. HCl (1 : 1), also by charcoal in the cold. White solid from EtOH–AcOH aq.; m. p. 226° (decomp.) after three crysts. (Lewis and Bent, *loc. cit.*, record no change at 260°) [Found: As (iodometric), 24·6; N, 12·7. Calc. for $C_9H_{12}O_5N_3As$: As, 23·7; N, 13·3%].

p-*Arsonoanilinomalonbismethylamide* (I; R = Me) was prepared by the above method from 3·24 g. of bromomalonbismethylamide and separated after 15 min. White plates, darkening at 295°, from EtOH–AcOH aq. (Found: As, 22·6; N, 12·0. $C_{11}H_{16}O_5N_3As$ requires As, 21·7; N, 12·2%).

p-*Arsonoanilinomalonbisethylamide*, similarly obtained from 3·67 g. of bromomalonbisethylamide, separated almost immediately. Fine white plates, unchanged at 300°, from EtOH–AcOH aq. (Found: As, 20·9; N, 11·1. $C_{13}H_{20}O_5N_3As$ requires As, 20·1; N, 11·3%).

p-*Arsonoanilinomalonbis*-n-*propylamide*, prepared from 4·11 g. of the amide in presence of 5 c.c. of EtOH, separated after 10 min. Lustrous platelets from 50% EtOH. Rapidly heated, it gradually darkens above 265° (Found: As, 19·0; N, 10·1. $C_{15}H_{24}O_5N_3As$ requires As, 18·7; N, 10·5%).

p-*Arsonoanilinomalonbis*-n-*butylamide*, prepared from 4·54 g. of the amide and 10 c.c. of EtOH, separated after 20 min. Small plates from 50% EtOH; m. p. 293° (decomp.) after darkening at 270° (Found: As, 18·2; N, 9·5. $C_{17}H_{28}O_5N_3As$ requires As, 17·5; N, 9·8%).

p-*Arsonoanilinomalonbis*iso*butylamide*, prepared in the same way as its isomeride, separated after 1 hr. Small clusters, unchanged at 260°, from 50% EtOH (Found: As, 18·2; N, 9·5%).

Malonbis-n-*amylamide*, $CH_2(CO{\cdot}NH{\cdot}C_5H_{11})_2$. Ethyl malonate (10·4 g.) and *n*-amylamine (10 g.) in a sealed tube formed a solid mass over-night and were then heated for 5 hr. at 120°. Cryst. from MeOH and then from petroleum (b. p. 100—120°), the product formed white plates, m. p. 128° (Found: N, 11·4. $C_{13}H_{26}O_2N_2$ requires N, 11·6%).

Bromomalonbis-n-*amylamide*, $CHBr(CO\cdot NH\cdot C_5H_{11})_2$. The preceding amide (7·5 g.) in $CHCl_3$ (25 c.c.) was brominated (1·5 c.c. Br, 15 c.c. $CHCl_3$) at 40—50°. The $CHCl_3$ was evaporated, and the semi-cryst. residue dissolved in EtOH; slight dilution with H_2O pptd. long prismatic needles, m. p. 98° (Found: N, 8·9; Br, 24·7. $C_{13}H_{25}O_2N_2Br$ requires N, 8·7; Br, 24·9%).

p-*Arsonoanilinomalonbis*-n-*amylamide* (I; R = C_5H_{11}) was prepared, like the lower homologues, from 4·97 g. of the bromoamide and 15 c.c. of EtOH; it separated after ½ hr. Small plates from much 50% EtOH; m. p. 297° (decomp.) after darkening at 275° (Found: As, 16·7; N, 8·9. $C_{19}H_{32}O_5N_3As$ requires As, 16·4; N, 9·2%).

Malonbisisoamylamide, prepared in the same way as its isomeride, crystallises from dil. EtOH or petroleum (b. p. 100—120°) in clusters of fine needles, m. p. 74° (Found: N, 11·3%).

*Bromomalonbis*isoamylamide, prepared from the preceding compound (2 g.) and Br (0·42 c.c.) in warm AcOH (14·2 c.c.) and pptd. after 10 min. by ice-water (200 c.c.), crystallised from dil. EtOH in fine prismatic needles, m. p. 110° (Found: Br, 24·7; N, 8·6%).

p-*Arsonoanilinomalonbisisoamylamide* was prepared like the isomeride and separated after 1 hr. Clusters, unchanged at 260°, from much 50% EtOH (Found: As, 16·8; N, 8·9%).

Ethyl p-*arsonoanilinomalonate*, $H_2O_3As\cdot C_6H_4\cdot NH\cdot CH(CO_2Et)_2$. A mixture of 1·74 g. of *p*-arsanilic acid in 7·75 c.c. of *N*-NaOH, 3·6 g. of bromomalonic ester, and sufficient boiling EtOH to complete solution was boiled for several hr., and the liquid evaporated; the residue crystallised from a little hot H_2O in fine white needles, m. p. 230° (decomp.). The yield was poor [Found: As (as $Mg_2As_2O_7$), 19·5; N, 3·9. $C_{13}H_{18}O_7NAs$ requires As, 20·0; N, 3·7%].

Methylbromomalonamide, $CMeBr(CO\cdot NH_2)_2$. Methylmalonamide (Meyer and Bock, *Annalen*, 1906, **347**, 98) was brominated in AcOH in the same way as malonbis*iso*amylamide. The product, which crystallised from the conc. solution, was washed with EtOH and Et_2O and recrystallised from hot EtOH; small needles, m. p. 165° (Found: Br, 40·9; N, 14·3. $C_4H_7N_2Br$ requires Br, 41·0; N, 14·4%).

Ethylbromomalonamide, similarly prepared from ethylmalonamide (Freund and Goldsmith, *Ber.*, 1888, **21**, 1245) and pptd., after conc., by Et_2O, formed fine needles, m. p. 160°, from EtOH (Found: Br, 38·1; N, 13·3. $C_5H_9O_2N_2Br$ requires Br, 38·2; N, 13·4%).

Ethylmalonbismethylamide, $CHEt(CO\cdot NHMe)_2$. Ethyl ethylmalonate was shaken with 33% aq. NH_2Me until the mixture became homogeneous. Long white needles separated on standing and were recrystallised from petroleum (b. p. 100—120°). The product, m. p. 177°, was readily sol. in EtOH, $CHCl_3$, and AcOH and less sol. in H_2O and petroleum (Found: N, 17·6. $C_7H_{14}O_2N_2$ requires N, 17·7%).

Ethylbromomalonbismethylamide, $CEtBr(CO\cdot NHMe)_2$, was prepared in the same way as bromomalonbis*iso*amylamide. After evaporation of the AcOH the residue crystallised from C_6H_6 in fine needles, m. p. 130° (Found: Br, 33·5; N, 11·9. $C_7H_{13}O_2N_2Br$ requires Br, 33·7; N, 11·8%).

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